Original Article

Efficacy of topical azathioprine and betamethasone versus betamethasone-only emollient cream in 2-18 years old patients with moderate-to-severe atopic dermatitis: A randomized controlled trial

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Abstract

Background: Atopic dermatitis is a chronic skin disease with increasing prevalence worldwide and a considerable burden especially among children. To circumvent the problems related to oral azathioprine (AZT) we aimed to evaluate its topical variant and assess its efficacy in patients aged 2–18.

Materials and Methods: In a single-blind trial, we randomized the patients into two groups, one treated with topical emollient containing AZT and betamethasone (BM), and the other treated solely with topical emollient of BM. The treatments were administered twice a day for 8 weeks in both groups. The efficacy, recurrence, and the presence of side effects were evaluated using SPSS 20.

Results: The amount of reduction in severity scoring for atopic dermatitis (SCORAD) score was significantly greater in the group treated with the topical AZT ($P = 0.024$). Incidentally, there were no difference between two treatments in difference in proportions of recurrence and adverse effects as well as SCORAD reduction in subgroups of sex and age (all $P > 0.05$).

Conclusions: Our results showed the superiority of topical AZT over BM with a low recurrence and adverse effects. No expectation of severe side effects, like those of oral AZT, is the major advantage of topical AZT. The sample size was an issue in uncovering the value of AZT in the subgroups. Conducting prolonged studies of quality-of-life and comparing the topical AZT potency relative to the common alternatives are recommended areas of future work.

Key Words: Atopic, azathioprine, child, clinical trial, dermatitis

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INTRODUCTION

Atopic dermatitis (AD) is a chronic or relapsing inflammatory disease of skin and more than half of patients develop asthma and allergic disorders.[1-3] AD closely matches regional variations of hay fever with various documented risk factors.[4-7] Due to increasing

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prevalence during past decades, it has become an important clinical problem in both developed and developing countries, especially in infants and young children of recent generations.[1,5,8] AD affects 1–3% of adults and more than 10% of children in developed countries and the incidences are increasing.[1,4,6] In the study by The International Study of Asthma and Allergies in Childhood, it has been reported that the annual increase in the prevalence of AD in Iran was 0.13 and 0.30 for 6–7 and 13–14 years age groups, respectively.[9] In addition to high economic burden, it has been shown that both AD symptoms and secondary infections result in the reduction of the quality-of-life in all age groups, especially in patients with moderate or severe disease.[3,8] The burden is higher in children where in addition to patient's life, family life, parenting, and spousal relationships are affected by AD.[3]

There is a variety of therapeutic options for AD. Topical steroids are routinely used treatment especially in mild to moderate AD. Atrophy, telangiectasia, glaucoma, and adrenal suppression are common side effects of topical steroids, particularly if used for a long period. For resistant and severe AD, oral steroids could be prescribed. However, due to serious side effects and severe rebound, long-term use of oral corticosteroids should be avoided.[10] Recommended second-line treatments of oral cyclosporine and narrow-band ultraviolet B have shown to be effective but there are concerns over toxicity for long-term use.[11] The effectiveness and long-term safety of topical calcineurin inhibitors in moderate-to-severe disease are yet to be established.[11]

Several studies have shown that azathioprine (AZT) might be effective for moderate-to-severe AD in adults and children.[12-14] The advantage of this drug is that it can be used continuously. Although AZT is a safer drug for long-term use, it does have several side effects including myelosuppression, fatigue, nausea, myalgia, hypersensitive syndrome, liver dysfunction, hepatotoxicity, and susceptibility for infection. Its main long-term side effect, at least theoretically, is the development of lymphoma.[4,15] In general, due to their side effects, using immunosuppressive drugs is limited to severe and resistant cases.

The usefulness of topical AZT has been previously shown in oral graft-versus-host disease and in oral autoimmune diseases.[16] Tashtoush *et al*. proved AZT absorption through rat skin and suggested it as a potential topical treatment for some dermatological disorders with minimum side effects.[17] Meggitt *et al*. conducted a randomized controlled trial in adults of age 16–65.[11] They used oral AZT or placebo along with optimum topical therapy and reported a relevant improvement from AZT over placebo in moderate-to-severe disease in patients with both normal and heterozygous range TPMT activity. The improvements were in patient-reported itch, area of involvement, global assessment, and quality-of-life. Furthermore, there has been no bone-marrow toxicity in heterozygotes.

Schram *et al*. reported same improvements for methotrexate and oral AZT in treatment of severe atopic eczema in adults with no serious side effects in the short-term.[18]

Hughes *et al*. assessed the use of oral AZT in a long-term of 18-year.[19] Out of 37 patients, 15 (40.5%) achieved remission in median period of 5 months and in only 5 patients the side effects lead to withdrawal.

Recent studies have shown the benefit of oral AZT in treatment of infantile AD. There is a variety of side effects following oral use of AZT and other systemic immunosuppressives in treatment of recalcitrant AD and the need for more studies in efficacy and side effects of its topical variant is growing. Due to high costs, lowered quality-of-life, emotional and social problems related to childhood AD, as well as clinical complications arising from currently used treatments, this prospective interventional study aimed to compare the efficacy of combined therapy with topical AZT and betamethasone (AZT + BM) emollient cream versus monotherapy with topical BM (BM-only) emollient cream in 2–18 years old patients with moderate-to-severe AD.

MATERIALS AND METHODS

Design

This study was a prospective, single-blinded, parallel-group, randomized controlled trial carried out in Skin Diseases and Leishmaniasis Research Center, Isfahan University of Medical Sciences, Isfahan, Iran. The protocol was approved by the Medical Ethics Committee of the university. Demographic information and patient history of eligible patients were collected using a questionnaire. Then patients were randomly assigned to treatment and control groups. Disease severity was recorded before and after the commencing the treatment for each patient. Side effects of any kind were recorded for each patient during the treatment period.

Patients, randomization, and outcomes

This study was conducted in teenagers and children (age between 2 and 18) with moderate or severe AD, unresponsive to common treatments (such as topical

corton) after at least 6 months, not receiving treatment interacting with AZT during the past month, and without history of liver or BM disorders. A patient was considered to be AD if he/she qualified at least 3 items out of each major (4 items) and minor criteria (23 items) as described in the protocol. After identifying an AD patient, written informed consent was obtained from his/her parents. Patients' contraindications were examined and recorded by a physician. If the results of liver enzyme and CBC with differential tests were normal, the patient randomly was assigned to one arm of the study by asking his/her parents to randomly pick a card from the vase containing 35 + 35 cards in two colors. Each patient was given 2 tubes of 15 gr and was asked to use the containing cream on lesions, except those of the face, twice a day for 8 weeks. The active treatment group received emollient cream containing BM and AZT and the control group received the emollient cream containing BM only. Each patient was checked after 1-week from initiation of the treatment for any side effects. The severity scoring for atopic dermatitis (SCORAD) was used to determine dermatitis severity before and after the administration of the treatment for each patient.[20] Based on rule of 9's for children, this score ranges from 0 to 103 for patients under study where scores within the range 26–50 and 51–103 represent a moderate and a severe disease, respectively. SCORAD is a combination of objective items including affected area and intensity of the lesions (erythema, edema/induration, excoriation, oozing/crusting, lichenification, and dryness) and subjective items of extent of pruritus and sleep loss on a visual analog scale.[18] The onset of any disorder in patients of the active treatment group and/or the parents unwillingness to follow the trial anymore, were exclusion criteria in this study.

SCORAD score was determined for each patient at baseline and after the treatment period was completed. Also, recurrence and existence of any side effects were recorded after a month of the treatment. Any pronounced local irritation, hives, and intense itching are considered as recurrence.

Blinding

Both creams were prepared in a same color and package and the patients were not aware of the treatment they were receiving. However, the treatment group was not blind to the treatments.

Formulation

Betamethasone is 9a-fluoro-1 1 p, 17a, 2 1-trihydroxy-16P-methylpregna-1, 4-diene-3,20-dione (378-44-91). Into a separatory funnel 0.1–2.0 ml aliquots of 0.10 mdml BM solution were pipette 4 followed by 3 ml of 5 × lo9 M reagent I or I1 and I5 ml 2.0 M H_2SO. The solution was diluted to 20 ml with water, and 10 ml of chloroform or benzene, using reagent I or 11, respectively, was added to extract the precipitated complex. After shaking for 2 min, the mixture was centrifuged for 1-min at 2000 rpm. After separation of the two layers, the absorbance of the chloroform or benzene extract was measured at 588 and 677 nm for the charge-transfer complexes formed using I and 11 respectively, against a reagent blank (I or II) prepared by the same manner.

For determining BM and AZT in pharmaceutical formulations, the required amount of pharmaceutical product containing about 50 mg of each drug was extracted into 50 ml hot chloroform. A suitable aliquot was analysed using the above procedure. The powder of AZT is a pale-yellow powder, practically insoluble in water and in alcohol. It is soluble in dilute solutions of alkali hydroxides, dimethyl sulfoxide and polyethylene glycol 400 and sparingly soluble in dilute mineral acids. It was formulated in the emollient base containing emu oil, cetyl alcohol, triethanolamine, stearic acid, glycerin, propylene glycol and water. The BM for control group was prepared using the same emollient base. In addition to being moisturizer, emu oil is anti-inflammatory and increases the absorption of the topical lotions.

The active treatment group received the emollient cream containing AZT 4% and BM 0.05% and the control group received the emollient cream containing BM 0.05% alone.

Statistical analysis

Required sample size was calculated for significance level of 95% to achieve the power of 80%. To avoid the estimation of remission prevalence following common treatments, it was considered to be 50% that gives the maximal sample size. We used minimal clinically important difference in remission percent as 35%. This gave $n = 35$ for each arm. The data were analyzed using SPSS 20 (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Descriptive statistics were described as mean ± standard deviation. Recurrence, side effects, and the SCORAD score changes were compared between two arms and subgroups and sex using Chi-square test and analysis of covariance. Due to small sample size in subgroups of age, we calculated the reduction in SCORAD score for each patient and used nonparametric Mann–Whitney U-test to compare SCORAD score changes in two groups. Results with $P < 0.05$ were considered statistically significant.

RESULTS

Of 70 patients registered at the beginning of the study, 3 individuals in AZT + BM group and two patients in

BM-only group were lost to follow-up due to unknown reasons and were replaced by new patients [Figure 1]. The other participants complied with the protocol. Patient recruitment and follow-up were between December 2013 and June 2014.

There were 17 (48.6%) and 18 (51.4%) male participants in AZT + BM and BM-only arm. The mean age of patients was 9.05 ± 4.98 and 8.68 ± 4.65, respectively with a range of 2–18 in both groups ($P = 0.74$).

There were two patients with mild itching and two patients with mild hives in AZT + BM group after 1-week from the initiating of the treatment. In control group, three patients experienced irritation and two patients had itches. These symptoms subsided within 2 weeks and no exclusion was required. The difference in proportion of patients with adverse effects was not statistically significant ($P > 0.99$).

The recurrence of the disease 1-month after stopping the treatment occurred for 11 (31.4%) and 15 (42.9%) patients in intervention and control groups, respectively. The proportion of recurrence in two groups was not statistically different ($P = 0.32$).

Figure 2 shows the profiles of change for case and control groups. Clearly, the mean reduction in SCORAD score in AZT + BM group is greater than BM-only group.

For AZT + BM group, the mean SCORAD scores at baseline and after the treatment were 36.22 ± 9.53 and 26.68 ± 6.96 ($P < 0.001$). For BM-only group, these were 35.48 ± 8.77 and 28.17 ± 7.57, respectively ($P < 0.001$). Mean reduction of – 9.54 ± 5.40 in SCORAD scores for AZT + BM group was significantly greater than that of – 7.32 ± 3.53 for BM-only group ($P = 0.024$).

We conducted further analyses in predefined subgroups of patients. We considered subgroups of sex and age in three categories of 2–6, 7–12, and 13–18 years old. The baseline measurements and subgroup analysis results are shown in Table 1.

There was no statistically significant difference between baseline measurements of two groups. Obviously, the reduction in SCORAD score in AZT + BM group was greater than that of BM-only group in all subgroups. However, the difference in change profiles between two groups was statistically significant for none of subgroups ($P > 0.05$).

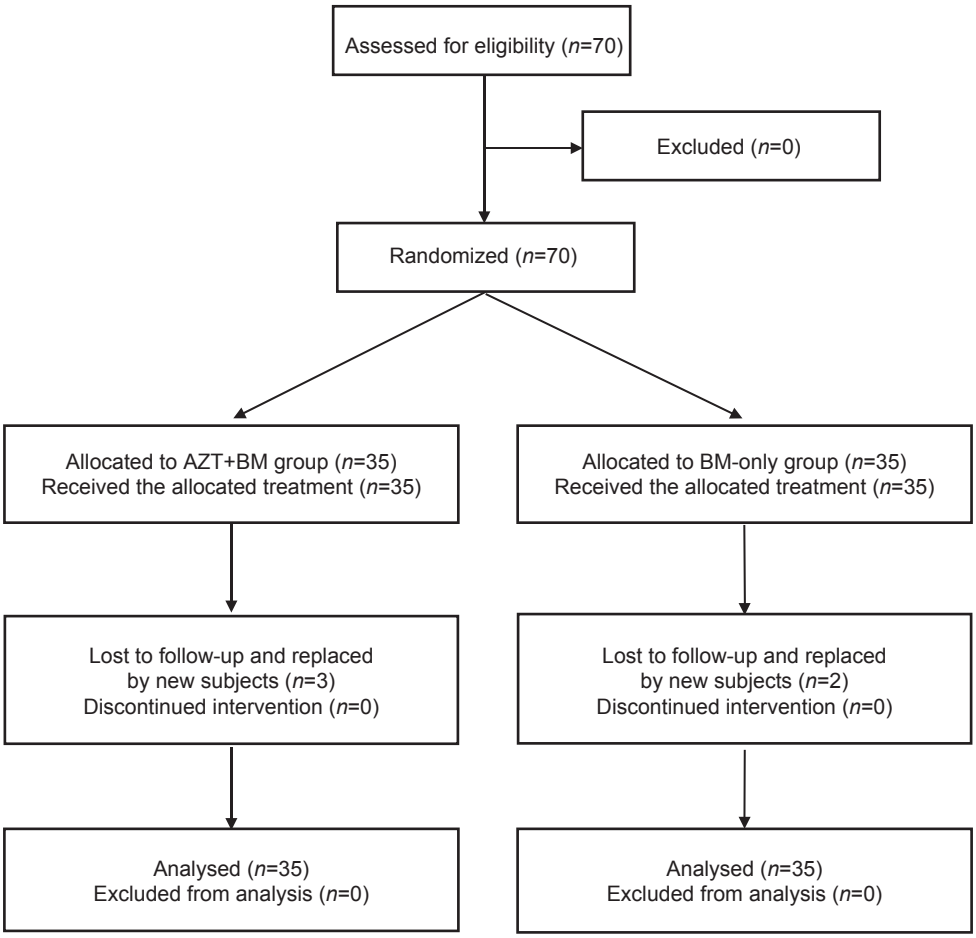

Figure 1: Study design

Table 1: Baseline measurements and subgroup analysis results

Subgroup	Treatment group	Baseline	After intervention	Difference	*P**
Males	AZT + BM (*n*=17)	38.58±8.83	27.64±6.04	−10.94±6.22	0.14
	BM-only (*n*=18)	34.11±9.22	26.72±8.34	−7.38±3.25	
Females	AZT + BM (*n*=18)	34.00±9.88	25.77±7.80	−8.22±4.25	0.10
	BM-only (*n*=17)	36.94±8.28	29.70±6.55	−7.23±3.91	
2-6 years old	AZT + BM (*n*=12)	34.08±6.74	25.16±5.96	−8.91±4.88	0.27
	BM-only (*n*=13)	34.30±7.69	27.30±6.43	−7.00±4.06	
7-12 years old	AZT + BM (*n*=13)	37.53±11.16	27.07±6.82	−10.46±6.47	0.25
	BM-only (*n*=14)	33.00±7.55	25.21±5.54	−7.78±3.74	
13-18 years old	AZT + BM (*n*=10)	37.10±10.60	28.00±8.51	−9.10±4.81	0.63
	BM-only (*n*=8)	41.75±10.31	34.75±9.05	−7.00±2.39	

*For the difference in SCORAD score changes between treatment groups in each subgroup. AZT + BM: Azathioprine and betamethasone group, BM-only: Betamethasone-only group, SCORAD: Severity scoring for atopic dermatitis

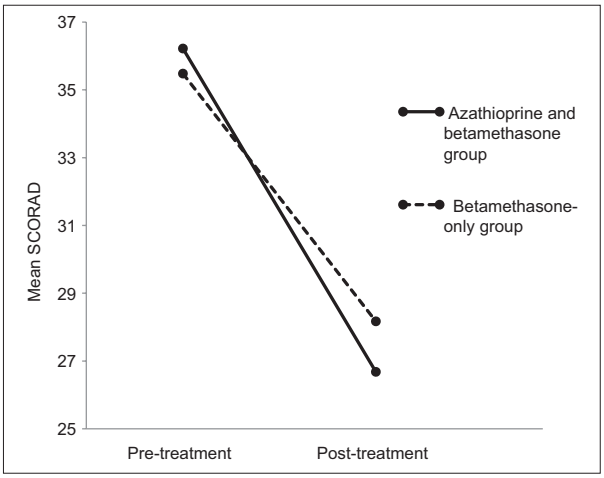

Figure 2: Mean severity scoring for atopic dermatitis profiles for azathioprine and betamethasone group and betamethasone-only group

DISCUSSION

The results of this study suggest that topical AZT could be a better alternative to commonly used therapies of childhood moderate-to-severe AD, with no excess recurrence or side effects.

The burden of childhood AD is increasing worldwide.[21] The occurrence of various problems is common for children and their parents. The scaly weepy skin may prohibit parents from normal bonding and interaction with their child and this can result in emotional and psychological problems in the child. The condition is more difficult in preschoolers where peer relationships can be affected by the appearance ensued from AD.[21] Some studies have reported that AD has an impact on the family's quality-of-life is greater than that of diabetes.[22] Kemp reported that the family stress due to care of children with moderate-to-severe atopic is greater than type 1 diabetes.[23] The burden becomes much more considerable if the economic costs are added to previously mentioned problems.[21] The high burden of childhood AD on one hand and complications related to current therapies, on the other hand, puts a great demand on search for safer and cheaper treatments for childhood AD.

Early diagnosis, testing for food and environmental exposures as causative factors, and putting avoidance measures into action could prevent or modify the occurrence of AD. Other factors such as breast-feeding for the first 6 month of the child's life could also be considered.[21]

There are currently various treatments for AD and their impacts on various aspects of skin functionality have been documented. Topical corticosteroids, fluticasone propionate, BM, pimecrolimus, and tacrolimus are amongst the others that their effects have been investigated previously.[24-28] Each treatment has its own merits and demerits such as severe complications in long-term use and impairments in skin barrier function and biophysical properties.

The benefit of oral AZT in moderate-to-severe AD has been previously established. In an 18-year follow-up study, Hughes *et al.* reported a promising proportion of 60% remission in 37 severe AD patients.[19] Meggitt *et al.* conducted a randomized controlled trial and found that in addition to disease activity, the improvements in patients' reported quality-of-life and clinical symptoms were also significantly greater in patients treated with AZT.[11]

Azathioprine is considered as an alternative to other second-line treatments such as cyclosporine in childhood AD.[29] However, the target cells and its exact mechanism are not fully understood.[30] Serious side effects, especially if used for a long-term, have limited its approval as a common treatment to AD.[29] Although some side effects such as toxicity are claimed to be dose-dependent and could be reduced by individualized adjustments to TPMT activity levels, the benefits of AZT may not appear until 2–3 months

after treatment onset and this prohibits its short-term prescription.[15,19,31]

Azathioprine is inexpensive and since its topical variant is not expected to be absorbed into the systemic circulation, it may be preferred to oral one. Tashtoush *et al*. proved the absorption of AZT via rat skin but there is no study in the literature to evaluate its efficacy and safety in human setting. In this study we administered topical AZT for severe AD in children for the first time. The results showed its superiority over active placebo with no elevation in recurrence or adverse effects. However, the difference between the AZT and placebo was not statistically significant in various subgroups of the patients. This could be a result of small sample size in predefined subgroups.

There are some limitations in this study one of which is small sample size. Conducting a similar study in a larger population may reveal subgroups that benefit more from AZT. The second is the rather short periods of patient follow-up. Studies on patient reported quality-of-life and with a prolonged period could clarify the merits of topical AZT over its oral variant and other alternatives. The relatively short follow-up period is another limitation. Noninferiority studies comparing topical AZT to oral AZT and the other second-line alternatives are some areas of future work. Assessing and comparing more aspects of skin functionality would be desirable that demand trials in a larger scale.

CONCLUSIONS

This study is the first on evaluating the efficacy of topical AZT in human subjects. Topical AZT significantly decreased the SCORAD score and performed better than BM. Large sample studies with longer periods are needed to provide more information on its pros and cons relative to its oral variant in moderate-to-severe childhood AD.

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