Original Article

Efficacy and Safety of Methotrexate and Prednisolone in the treatment of Severe Alopecia areata

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Abstract:

Background: Alopecia areata is a chronic disorder of hair follicles of unknown aetiology with clear autoimmune components. Several therapeutic options have been suggested; however, no treatment can modify the disease course. Recently Methotrexate introduce as a safe and effective corticosteroid-sparing agent in several autoimmune diseases as well as in alopecia areata. **Objectives:** To evaluate the efficacy and safety of methotrexate and prednisolone in severe alopecia areata. **Methods:** In a prospective consecutive case series study, 15 patients were evaluated who had severe alopecia areata (AA) with a mean duration 7.60 years and were treated with 15 mg/weekly methotrexate (MTX) with 20 mg /day oral Prednisolone. All patients were recruited from the outpatient department of Dermatology and Venereology at Shaheed Suhrawardy Medical College and Hospital, Dhaka and two private dermatology clinics from January 2015 to December 2019. **Results:** A total regrowth of terminal hair was regarded as a success. Success was achieved in 73.33% of patients. Within a mean follow-up of 14.86 months after treatment, relapse occurs in 6 patients (focal/multifocal in 4 patients, diffuse loss in 2 patients). Relapse resolved by potent local corticosteroid application for focal/multifocal cases and restarting the previous dosage of medication for diffuse cases. Complications were minor and resolved spontaneously.
Conclusion: Methotrexate plus oral corticosteroid appears to be a promising, inexpensive and safe medication for the treatment of severe alopecia areata.
Keywords: Methotrexate, Prednisolone, alopecia areata, efficacy.

Introduction:

Alopecia areata (AA) is a non cicatricial, autoimmune variety of hair loss that affects both sexes and all ages with an incidence of 0.1-0.2% and an estimated lifetime risk of 1.7 among the general population.[1] Depending on the number, distribution and extent of involvement, AA may be unifocal, multifocal, ophiasis, totalis, Universalis, sisaipho (ophiasis inversus), reticular and diffuse.[2]

Pathogenesis involved in the AA includes sensitization of T lymphocytes, particularly CD8 cells. Consequently release of several Th1 cytokines IL alpha, IL beta and TNF alpha ultimately inhibit the growth of hair follicles and arrest hair synthesis with early termination of anagens. The natural history of AA, as well as the possible factors influencing its course and extent, remains unknown, making the outcome of the disease as often as not unpredictable on presentation.[3]

About 34%-50% of patients with AA will recover within one year. While 14% -25% progress to total hair loss on the scalp (Alopecia totalis, AT) or even on the entire body (Alopecia Universalis, AU). In AT, AU spontaneous full recovery is rare.[4-5]

Several treatment options have been tried in AA

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patients but their results remain rather disappointing, questionable and temporary.[6] Systemic corticosteroids, are relatively common options for AA patients but required unacceptably high maintenance doses.[7] Recently MTX was introduced as a safe and effective corticosteroid-sparing agent in several autoimmune disorders as well as in AA.[8-9] Anti-inflammatory action of the MTX inhibits white blood cells accumulation, leads to reduction in the TNF alpha and IFN- gamma synthesis, and inhibits a variety of monocytes, macrophage and T-cell activities-all these activities improve the course of AA.[10] several authors claim MTX alone or in combination with oral corticosteroids has been efficacious, safe and well tolerated in patients with severe AA.[11-14]

The current prospective study aimed to evaluate the efficacy of MTX in combination with oral corticosteroid (Prednisolone) in treating patients with severe AA.

Materials and Method:

Study design and patients: In this prospective, consecutive case series study, 15 patients with intractable, extensive AA (7 patients with AT, 4 patients with AU, 4 patients with DA; Table I) (with no or poor response to conventional treatments) were recruited from the outpatient department of Dermatology and Venereology at Shaheed Suhrawardy Medical College and Hospital, Dhaka and two private dermatology clinic during January 2015 to December 2019.

The following were excluded from enrollment in the study: pregnant or breastfeeding women, patients who were planning to have a child, hepatic or renal insufficiencies, active TB patients, ulcerative colitis, and body dysmorphic disorders. Furthermore, patients were informed of possible side effects of MTX and corticosteroids and started therapy after taking written consent from patients. The ethical committee of ShSMCH approved the study.

Treatment regimen:

Each patient was treated with oral MTX 15 mg once weekly after a test dose of 5 mg in the first week and tablet prednisolone 20 mg daily. Three patients (no 7, 10, 15) needed a dose increment of prednisolone 10 mg/day and an ultimate dose of 30 mg/day.

MTX was continued at the same dose until 18 months after the beginning of hair regrowth during this time prednisolone had been successfully tapered (after full hair regrowth) to the lowest maintenance dose or fully withdrawal. MTX doses were then gradually tapered and then later stopped.

Result:

Table I: Characteristics of the studied patients with Alopecia areata (n=15) Out of 15 enrolled patients 10 were females and 5 were males with a mean age of 34.07 ± 8.89 (21-49) years at the time of presentation, mean duration of the disease was 7.60 ± 3.85 (2-13) years (Table I).

Characteristics	Frequency	Percent
Type of Alopecia		
○ AT	7	46.7
○ AU	4	26.7
○ DA	4	26.7
Sex		
○ Male	5	33.3
○ Female	10	66.7
○ Age (Years)		
○ 21-30	5	33.3
○ 31-40	6	40.0
○ 41-49	4	26.7
Mean ± SD (Min-Max)	34.07 ± 8.89 (21-49)	
Duration of diseases		
○ 2-5 years	5	33.3
○ 6-9 years	4	26.7
○ 10-13 years	6	40.0
○ 10-13 years	6	40.0
Mean ± SD (Min-Max)	7.60 ± 3.85 (2-13)	40.0

* AT: Alopecia totalis, AU: Alopecia uiversalis, DA: Diffuse alopecia

Table II: Demographics and the results of treatment with Methotrexate and prednisolone in the studied patients with Alopecia areata

Pt. no. sex/ Age	Type of alopecia *	Duration of diseases (yrs)	Initial MTX dose (mg/dl)	Initial prednisolone dose mg/day	Hair regrowth (grade)	Time required for onset regrowth(m)	Follow up duration (m)	Compli cations	End MTX dosage (mg/wk)	End prednisolone dosage (mg/day)	relapse
1. F/22	AT	2	15	20	iv	3	20	-	10	0	-
2. M25	DA	6	15	20	ii	3	18	acne	10	0	-
3. F/21	AT	3	15	20	iv	2	17	-	7.5	5	Yes multifocal
4. M/31	AU	5	15	20	iv	2	12	acne muscle cramp	10	0	-
5. F/27	AT	3	15	20	iv	4	8	Acne	5	5	Yes multifocal
6. F/26	AT	2	15	20	iv	2	9	-	5	5	-
7. F/39	DA	11	15	20	iv	4	31	hyper tension	10	several other diseases	-
8. M/33	AU	10	15	20	iv	3	11	hyper tension	15	0	-
9. F/37	AT	11	15	20	i	4	6	–	15	5	yes /focal
10. F/41	DA	9	15	20	ii	2	30	muscle cramp	10	10	yes diffuse
11. F/48	AT	13	15	20	iv	3	28	weight gain	15	5	–
12. F/43	AU	12	15	20	iv	3	5	acne	15	7.5	yes/ focal
13. F/33	DA	11	15	20	i	2	4	–	10	0	–
14. M/36	AU	9	15	20	iv	2	4	weight gain	105	0	yes multifocal
15 F/49	AT	7	15	20	iv	2	20	wt g	15	7.5	-

*AT: Alopecia totalis, AU: Alopecia uiversalis, DA: Diffuse alopecia

The mean of the follow-up was 14.87 ± 9.43 (4-31) months (table III). Hair regrowth began in all patients after a mean period of 2.73 ± 0.80 months ranging from 2 to 4 months. Eleven out of 15 patients (73.33%) achieved total hair regrowth (grade IV), while in 2 patients the grade of hair regrowth was II and another 2 had grade I hair regrowth (Table III).
Relapse was encountered in 6 patients (40%) within a month after treatment. In 4 cases (Patients 3,9,12 and 14) the relapse was in the form of focal, which resolved after potent local corticosteroid application. In 2 cases (Patients 5 and10) the relapse was diffuse, which resolved after restoring to the previous dosages of medications. Minor complications were reported in 10 patients (66.66%) including acne (n=4), muscle cramp (n=2), herpes infection (n=1), hypertension (n=1), weight gain (n=3). Fortunately, complications were mild and need not stop the treatment. The results of laboratory tests were all in the normal range.
Table III: Dose of MTX/prednisolone, outcome and complication of studied patients (n=15)

Characteristics	Frequency	Percent
Hair re growth (grade)		
○ I	2	13.3
○ II	2	13.3
○ IV	11	73.3
Time for the onset of diffuse regrowth (m)		
○ 2	7	46.7
○ 3	5	33.3
○ 4	3	20.0
Mean ± SD (Min-Max)	2.73 ± 0.80 (2-4)	
Follow up (m)		
Mean ± SD (Min-Max)	14.87 ± 9.43 (4-31)	
Complications†		
○ Acne	4	26.7
○ Muscle cramp	2	13.3
○ Hypertension	2	13.3
○ Weight gain	3	20.0
○ No complication	5	33.3
Relapse		
○ Yes	6	40.0
➢ Focal	2	33.3
➢ Multifocal	2	33.3
➢ Diffuse	2	33.3
○ No	9	60.0

†multiple responses

Figure (a-d) Photograph of a case of alopecia totalis before and after the treatment.

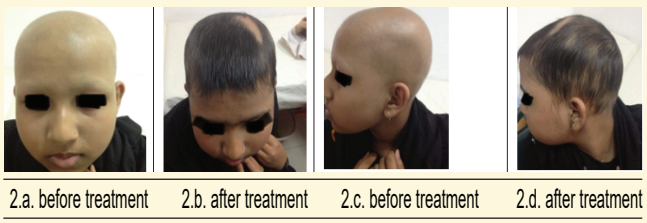

Figure 2 (a-d) Photograph of a case of alopecia universalis before and after the treatment.

Follow-up and assessment of efficacy:

Patients were monitored for the first three months every month and then were followed up every two months. Complete blood count, liver function tests, kidney function tests, fasting blood sugar, fasting lipid profile, and serum electrolytes were obtained at baseline and all visits. Evaluation of therapy was performed clinically and by using photographs.
The final clinical response was rated according to a grading system proposed by Hull and Norris (1988).[15]
Grade I: regrowth of vellus hair
Grade II: regrowth of sparse pigmented terminal hair
Grade III: regrowth of terminal hair with patches of alopecia
Grade IV: regrowth of terminal hair on the scalp
Only a total regrowth of the scalp terminal hair (Grade V) was considered "success".[11]

Discussion:

Though the self regrowth of hair for patchy alopecia is possible in 30–50% within the first 6–12 months of disease onset, and 66% of the patients will show complete remission within 5 years, relapse occurs in about 85% of cases and practically 100% in patients observed over 20 years.[16-18] Moreover, spontaneous recovery in chronic and diffuse alopecia is practically very rare.[16-18] Despite the non-controlled character of the current study, MTX in combination with a low dose of prednisolone was found to be effective in severe types of AA.

In the current study, the mean duration of AA was 7.60 years and all the conventional or non-conventional therapies were previously tried in vain. After a mean duration of 2.7 months, hair regrowth began in 11 patients (73.33%). It should be noted that success was defined strictly a total hair regrowth of grade IV according to the grading system proposed by HULL and Norris (1988).[15] Interestingly hair growth of Grade II and Grade I was achieved in the remaining equal 13.33 % of patients. So this rate of efficacy is near the success claimed by Firooz et al., where MTX plus Prednisolone was in severe AA (2013) and far more than the rate of total hair regrowth (64%) reported in a similar study by Joly P (2006).[19,10] Efficacy of the regimen used in this study also better than the other available treatments in AA patients.[20-26]

This high rate of success cannot be attributed to chance, because it is shown that at best only 10% of patients with long-term severe AA may be associated with spontaneous regrowth.4 During a mean follow-up of 14.86 months after starting the treatment 40% of patients relapsed (focal, multifocal and diffuse loss). Though this rate seems to be high, full recovery was retrieved simply after using potent local topical steroid application in focal areas, and in diffuse cases by restoring the previous dosages of medication. Minor complications were reported by 66.66% of the patients in our study. These less serious, self-limiting complications did interfere with neither the protocol of treatment nor the patient's compliance. Whether MTX plays just a corticosteroid-sparing role or it can be used individually as a single reliable treatment in patients with severe AA, is not well known.[11,27] According to available data, however, systemic corticosteroid therapy alone seems not effective against initiation, spread or relapse of severe AA and when complete regrowth is obtained, it rarely remains effective sufficiently.[28]

To the best of our knowledge, this is one of the few studies that examine the effects of treatment with MTX and oral corticosteroid in patients with extensive AA prospectively, quite unlike two similar available retrospective reports which used MTX with or without corticosteroid in these cases.[11,27]

It is acknowledged that the study had no control, small sample size and intermediate follow-up; however, the results were worthy of attention. But maintenance doses of MTX and oral Prednisolone are very much essential in these patients. So, regarding the duration of maintenance therapy, a fruitful recommendation should be made by further studies.

It should be emphasized that well being of life of the patients with severe AA is probably close to that of other chronic auto immune dermatoses such as psoriasis and eczema, which are commonly treated by MTX and or corticosteroids usually for the lifetime.[29-30] Treatment used in the current protocol was well tolerated with no serious adverse events. Potential side effects of long-term methotrexate therapy have to be taken into account.

So, even though the essentiality of further studies regarding long-term consequences of MTX –Corticosteroids combination in severe AA patients cannot be ignored, the results of the current study could not be sold short.

Further studies with emphasis on the patients' age, gender, skin type, presence of atopy or other diseases etc are also recommended in this regard.[31-33]

Conclusion: Oral Methotrexate in combination with prednisolone is an efficacious, safe, inexpensive and well-tolerated systemic treatment option in severe alopecia areata.

References:

1. Mc Donagh AJ and Tazi-Ahnini R. Epidemilogy and genetics of alopecia areata .Clin. Exp. Dermatol. 2002;27:405-409.
2. Rivitti E. Alopecia areata : a version and update.An Bras Dermatol.2005;80(1):57-68.
3. Alexis AF, Dudda- Subramanaya R and Sinha AA. Alopecia areata : Auto immune basisof hair loss.Eur.J.Dermatol. Nov-Dec 2004;14(6):364-70.
4. GipL, Lodin A and Molin L alopecia areata . A follow –up investigation of outpatient material.Acta Derm.Venereol. 1969;49: 180-188.
5. Tosti A, Bellavista S and lorizzo M. Alopecia areta: a long term follow-up study of 191 patients. J.Am. Acad. Dermatolol. 2006 Sep;55(3):438-41.
6. Misery l, Sannier K, Chastaing M and Le Gallic G. Treatment of alopecia areata with slfasalazine . J.Eur.Acad . Dermatol.Vnereol. 2007 Apr;21(4):547-8.
7. Madani S, Shapiro J. Alopecia areata update. J Am Acad Dermatol. 2000 Apr;42(4):549-66; quiz 567-70.
8. Gurean HM and Ahmed AR. Analysis of current data on the use of methotrexate in the treatment of pemphigus and pemphigoid. Br.J. Dermatol. 2009 Oct;161(4):723-31.
9. Perez A, Woods A, Grattan CE. Methotrexate: A useful steroid-sparing agent in recalcitrant chronic

urticaria. Br J Dermatol 2010;162:191-4
10. Joly P. The use of methotrexate alone or in combination with low doses of oral corticosteroids in the treatment of alopecia totalis or universalis. J Am Acad Dermatol. 2006 Oct;55(4):632-6.
11. Chartaux E and P Joly Long term follow –up of the efficacy of methotrexate alone or in combination with low doses of oral corticosteroids in the treatment of alopecia areata totalis or universalis.Ann. Dermatol.Venereol. Aug-Sep 2010;137(8-9):507-13.
12. Droitcourt C, Milpied B, Ezzedine K, Hubiche T, Belin E, et al. Interest of High-Dose Pulse Corticosteroid Therapy Combined with Methotrexate for Severe Alopecia Areata: A Retrospective Case Series. Dermatology. 2012;224:369-73.
13. Royer M, Bodemer C, Vabres P, Pajot C, Barbarot S, et al. Efficacy and tolerability of methotrexate in severe childhood AA. Br J Dermatol. 2011;165:407-10. 12.
14. Neves C, Jorge R, Barcelos A. A Teia de Toxicidade do Metotrexato. Acta Reumatol Port. 2009;34:11–34.
15. Hull SM and Norris JF. Diphencyprone in the treatment of lng-standing alopecia areta. Br.j. Dermatol. 1988 Sep;119(3):367-74.
16. Price VH. Treatment of hair loss. N Engl J Med. 1999 Sep 23;341(13):964-73.
17. Taylor CR, Hawk JL. PUVA treatment of alopecia areata partialis, totalis and universalis: audit of 10 years' experience at St John's Institute of Dermatology. Br J Dermatol 1995;133:914-8.
18. Bissonnette R, Shapiro J, Zeng H, McLean DI, Lui H. Topical photodynamic therapy with 5-aminolaevulinic acid does not induce hair regrowth in patients with extensive alopecia areata. Br J Dermatol 2000 Nov;143(5):1032-5.
19. Firooz A, Firoozabadi MR, Ghazisaidi B and Dowlati Y Concepts of patients with alopecia areata about their diseases.BMC Dermatol. 2005 Jan 12;5:1.
20. Behrens- Williams SC, Leiter U, Schiener R, Weidmann M, Peter RU, et al. The PUVA –turban as a new option of applying a dilute psoralen solution selectively to the scalp of patients with alopecia areata. JAm.Aead. Dermatol. 2001 Feb;44(2):248-52.
21. Yoshizawa Y, lzaki S, Kitamura K and Kawana S. Systemic immunothrapy with topical dinitochlorobenzene as additional treatment of alopecia areata. acta Dermato Venereol., Acta Derm Venereol 2002; 82: 136–157.
22. Tosti A, Piraccini BM, Pazzaglia M and Vincenzi C Clobetasol proprionate 0.055 under occlusion in the treatment of alopecia totalis/ universalis. J.Am .Aead. Dermatolol, 2003 Jul;49(1):96-8.
23. Kar B, Handa S, Dogra S and kkumar B Placebo-controlled oral puilse prednisolone theraply in alopecia areata .JAm.Acad Dermatol. 2005 Feb;52(2):287-90.
24. Farshi S, Mansouri P, Safar F and Khaibanloo SR Could azathrioprine be considered as a therapeutic alternative in the treatment of alopecia areata . A pilot study. 2010 Oct;49(10):1188-93.
25. Feldmann KA, Kunte C, Wollenberg A, Wolfe H. Is topical tacrolimus effective in alopecia areata universalis/ Br J Dermatol 2002;147:1031-2.
26. Higgins E, du Vivier A. Topical immunotherapy: unapproved uses, dosages, or indications. Clin Dermatol 2002;20:515-21.
27. Seiter S, Ugurel S, Tilgen W, Reinhold U. High-dose pulse corticosteroid therapy in the treatment of severe alopecia areata. Dermatology 2001;202:230-4.
28. Royer M, Bodemer C, Veabres P, Pajot C, Barbarot S, et al. Efficacy and tolerability of methotrexate in severe childhood alopeia areata. Br. J. dermatol. 2011 Aug;165(2):407-10.
29. Albdul kareem AS, Abahussein AA and Okoro A Severe alopecia areata treated with systemic corticosteroids. Int. J. Dermatol.1998 Aug;37(8):622-4.
30. Firooz A, Firoozabadi MR, Ghazisaidi B and Dowlati Y Concepts of patients with alopecia areata about their diseases.BMC Dermatol. 2005 Jan 12;5:1.
31. Babaeinejad S. Khodaeiani E and Fouladi RF. Comparison of therapeutic effects of oral doxycycline and azithromycin in patients with moderate acne vulgaris: What is the roe of age? J.Dermaol.Treat. 2011;22:206-210.
32. Navali N, Pourabolghasem S, Fouladi RFand Nikpour MA. Therapeutic effects of biguanide vs statin in poly cystic ovary syndrome : aA randomized clinical trial .Pak. J. Biol. Sci. 2011;14: 658-663.
33. Khodaeiani E, Fouiadi RF, Amirnia M, Saeidi M and Karimi ER. Topical 4% nicotinomide vs 1% clindamycin in moderate inflammatory acne vulgaris. Int , J,Dermatol.2013; 52: 999-1004.