

# Efficacy and Safety of Methotrexate in Combination with Mini Pulse Doses of Methylprednisolone in Severe Alopecia Areata. The Vietnamese Experience

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## Abstract

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**BACKGROUND:** Treatment of severe alopecia areata remains very difficult, especially in alopecia areata totalis and alopecia areata universalis. Methotrexate is known to be effective in the treatment of severe and chronic autoimmune disorders.

**OBJECTIVE:** To assess the effectiveness and safety of MTX in combination with mini pulse dose of methylprednisolone in the treatment of severe alopecia areata.

**PATIENTS AND METHODS:** The open, uncontrolled study compared pre-treatment and after-treatment. Thirty-eight patients (age 16-64) with severity AA (SALT score > 50 %) visiting National hospital of Dermatology and Venereology from April-2004 to September-2015 were enrolled. All patients received oral methylprednisolone 24mg/day for 3 consecutive days of a week in combination with oral MTX 7,5 mg weekly. This regimen is maintained up to 12 weeks and follow-up until to 6 months.

**RESULTS:** After 6 months, 60.5% of patients show complete hair growth (good response) and 18.4% shows the medium response. There is a significant SALT score reduction: mean baseline SALT score  $84.39 \pm 17.03$  compared to mean post-treatment SALT score  $24.19 \pm 29.42$ . Good clinical improvement noted in after 3 months. We do not observe any side-effects related to oral MTX and oral methylprednisolone, and no patients had to withdrawal treatment due to side-effects.

**CONCLUSION:** Combination Methotrexate and mini pulse dose of methylprednisolone are effective and safe in treatment severity alopecia areata.

## Introduction

Alopecia areata (AA) is one of the most common diseases of hair loss, the pathogenesis of the disease is still unknown but recently, it is considered an autoimmune disease [1], [2], [3], [4]. It is characterised by recurrent non-cicatricial hair loss that can affect any hair-bearing area such as the scalp, beard, eyelashes, and eyebrows. Patients usually start silently, develop persistently and relapse [5]. Although it is a benign condition and most patients

are asymptomatic, but it can cause emotional and psychosocial distress. Incidence varies according to race and geography. In the United States, an estimated 4.5 million people are infected. It accounts for 0.1 to 0.2% of the world population [6], [7]. The disease can occur at any ages and in both sexes, but predominantly in young people aged 15-45, rarely seen in older adults and young children. Male and females are affected equally, and the prevalence is almost the same for all ethnic groups [8], [9]. Some factors related to this disease included family, allergic, immunological, endocrine, psychological trauma or

infection.

Treatment of severe alopecia areata remains very difficult, especially in alopecia areata totalis and alopecia areata universalis [10], [11], [12], [13]. Corticosteroids are the most commonly used agents in the treatment of AA, especially in the extensive forms, but the success of these agents is controversial [4], [12], [14]. In several studies, they are reported that alone corticosteroid treatment is not effective and the relapse rate is still very high [12], [13], [15]. Methotrexate is known to be effective in the treatment of severe and chronic autoimmune disorders, and it is a safe and effective corticosteroid-sparing agent [16]. Recently, MTX combination with oral corticosteroid has been reported effect and safe in severe AA [17], [18], [19], [20]. So we want to assess the effectiveness and safety of MTX in combination with mini pulse dose of methylprednisolone in the treatment severe alopecia areata.

## Materials and Methods

**Study design and design:** Thirty-eight patients (age 16 -64) with severity AA (SLAT > 50 %) visiting NHDV from April-2004 to September-2015 were enrolled. The diagnosis of alopecia areata was based on clinical criteria. Severity alopecia areata patients were identified when SALT scores from 50% to 95% of the scalp area. Alopecia areata totalis (AT) is when hair loss from 95 to 100% of scalp area without hair loss in the body. Alopecia areata universalis (AU) means hair loss all of the scalp and in the body.

**Treatment regimen:** The regimen included oral methylprednisolone 24 mg/day for 3 consecutive days of a week in combination with oral MTX 7,5mg/week. This regimen is maintained up to 12 weeks and follow-up until to 6 months.

**Follow-up and outcome assessment:** The degree of hair loss was assessed by SALT (Severity of Alopecia Tool) score in before treatment and monthly (every 4 weeks) after treatment. Transaminase levels (AST, ALT) and complete blood count were performed before treatment and after 3 months of treatment (12 weeks). Photographs of hair loss area were taken for each visit and recorded in files. Evaluation of the efficacy treatment used SALT score and patient satisfaction.

- Good response: Hair grows well, thick, black, covering the area of scalp and body, patients are satisfied.

- Moderate response: hair grows thin, brown or white, partially covered, patients are satisfied.

- Poor response: hair does not grow, patients are not satisfied.

Follow the side effects: acne, hypertension, stomach pain, headache, nausea, elevation of transaminase levels, count blood cell.

Exclusion criteria included the patient who has SALT score < 50%, patients are contraindicated for MTX, steroids and the patient who has pregnant women or intended pregnancy and breastfeeding.

## Statistical analysis

The data were analysed by SPSS20.0 version. Results were reported as the mean ± standard deviation (SD) for the quantitative variables and percentages for the categorical variables. Analyses for normal distribution fitness were performed. Student t-test was used for intergroup comparison. Chi-square test was applied for the analysis of categorical variables. P values < 0.05 were considered to be statistically significant.

## Results

A total of 38 patients had severe alopecia areata, including 31 (82%) female and 7 (18%) males were enrolled in this study. The mean age of the patients was 29.61 ± 12.07 and the meandiseasedurationwas 26.47 ± 30.1 months. Eighteen patients (47.4%) had severe AA, and 9 patients (23.7%) had AT and11 patients (28.9%) had AU.



Figure 1: The effectiveness of treatment: patient at baseline (A); after one month of treatment (B); after 6 months of treatment (C)

Follow-up after 1 month of treatment showed that only 3 patients (7.9%) had a good response, 18 patients (47.4%) had a medium response, and 17 (44.7%) patients had a poor response.



Figure 2: The effectiveness of treatment: patient at baseline (A); after one month of treatment (B); after 6 months of treatment (C)

However, at the end of 3 months of treatment, 22 patients (57.9%) had hair re-growth completely, 9 patients (23.7%) had hair re-growth partially, and 7 patients (18.4%) had still a poor response.

After 6 months of follow-up in this study, we found 23 patients (60.5%) had a good response and 9 patients (23.7%) had a medium response, and in those patients had no new patch or recurrent after stopping treatment as presented in Table 1.

**Table 1: The efficacy of treatment every month**

Responses	1-month treatment	2-months treatment	3-months treatment	6-months treatment
Good response	7.9 (3/38)	47.4 (18/38)	57.9 (22/38)	60.5 (23/38)
Medium response	47.4 (18/38)	28.9 (11/38)	23.7 (9/38)	23.7 (9/38)
Poor Response	44.7 (17/38)	23.7 (9/38)	18.4 (7/38)	15.8 (6/38)
Total	38	38	38	38

The area of hair loss decreases in each visited, SALT score in before treatment was  $84.39 \pm 17.03\%$ , after 1-month treatment reduced to  $65.10 \pm 26.29\%$ , and decreased dramatically after 2-months treatment was  $45.67 \pm 28.21\%$  after 3-months treatment was  $29.97 \pm 29.67\%$ . At the end of the study, the area of hair loss according to SALT was  $24.19 \pm 29.42\%$  as shown in Table 2. No patients in our study had side effected related to oral corticosteroid and MTX.

**Table 2: The SALT score in every month follow-up**

SALT Score	Mean $\pm$ SD	P (before- after)
Before treatment	$84.39 \pm 17.03$	p < 0.05
After 1 month	$65.10 \pm 26.29$	
After 2 months	$45.67 \pm 28.21$	
After 3 months	$29.97 \pm 29.67$	
After 6 months	$24.19 \pm 29.42$	

## Discussion

This study shows that there is a significant clinical improvement when using a combination of methotrexate and mini pulse dose of methylprednisolone in treating alopecia areata, especially in the severe cases.

Over the past several years, the treatment of alopecia areata is very difficult; no therapy has long-term effects, the rate of recurrence is still high. Systemic corticosteroid was used in the treatment of hair loss in many years [21], [22]. This drug is effective, but the use of long-term drug causes many side effects [10], [14], [23], [24]. Joly (2006) was treated 22 patients had severe AA by using MTX and corticosteroid. These patients were treated with MTX alone (6 patients) or in combination with low dose oral prednisolone (16 patients). The dose of MTX varies from 15-25 mg/week; the dose of prednisolone varies from 10-20 mg/day. Results showed that the number

of patients with hair grows completely were 14/22 patients (64%). No side effects have been reported. A reported by Chateaux and colleagues (2010) found that using corticosteroids in combination with MTX resulted in hair growth in 63% of patients. The dosage of MTX is 15-25 mg/week; the average duration of treatment is 3 months [18]. Royer et al., study (2011), 14 children (eight girls and six boys) aged between 8 and 18 years (mean 14.7) treated with MTX. The mean maximal dose was 18.9 mg weekly (range 15-25 mg/week), and the mean duration of treatment was 14.2 months (range 1 to 31 months). MTX was considered as successful (regrowth > 50% of hair) for five of them [19]. Comparison with other authors' studies also suggests that response rates for combination therapy are very high [20]. These studies have shown MTX to be effective in treated severe AA, with good response rates from 57 to 64% [24]. Thus our study used this regimen for a better outcome. It also helps to reduce the side effects of daily corticosteroids and to prevent recurrence of hair loss after stopping the drug. The results of recent studies suggest that alopecia areata are more related to immune dysfunction due to the presence of TCD4 and TCD8-active lymphocytes around the progressive hair follicles. Therefore, treatment of hair loss by using immunosuppressive drugs has been shown to be effective [23], [25], [26], [27], [28].

In conclusion, our study showed that no patient had severe side-effected had to stop treatment, only 2/38 (0.05%) patients had a headache, 3/38 (0.07%) patients had to feel vomiting. The results of this study were suitable for different research. After 3 months, we stopped these drug and follow-up the patients in 3 months next, but in the patients who responded, no patients had recurred. Compared with other single steroid studies, the relapse rate was relatively high, maybe over 50% of cases [10], [14]. The recurrence rate in our study was much lower than that reported by Joly [17]. Thus, we think this may be a good approach that can be applied clinically as it is effective, especially in patients who do not respond to other methods.

## References

- Mitchell AJ, Krull EA. Alopecia areata: pathogenesis and treatment. *Journal of the American Academy of Dermatology*. 1984; 11(5):763-75. [https://doi.org/10.1016/S0190-9622\(84\)80450-8](https://doi.org/10.1016/S0190-9622(84)80450-8)
- Hedstrand H, Ekwall O, Michaëlsson G, Rorsman F, Kämpe O, Perheentupa J, Gustafsson J, Husebye E. Antibodies against hair follicles are associated with alopecia totalis in autoimmune polyendocrine syndrome type I. *Journal of investigative dermatology*. 1999; 113(6):1054-8. <https://doi.org/10.1046/j.1523-1747.1999.00778.x> PMID:10594751
- Olsen EA, Hordinsky MK, Price VH, Roberts JL, Shapiro J, Canfield D, Ducic M, King LE, McMichael AJ, Randall VA, Turner ML. Alopecia areata investigational assessment guidelines—Part II.

- Journal of the American Academy of Dermatology. 2004; 51(3):440-7. <https://doi.org/10.1016/j.jaad.2003.09.032> PMID:15337988
4. Alkhalifah A, Alsantali A, et al. Alopecia areata update. Journal of the American Academy of Dermatology. 2010; 62(2):191-202. <https://doi.org/10.1016/j.jaad.2009.10.031> PMID:20115946
  5. McDonagh AJ, Tazi-Ahni R. Epidemiology and genetics of alopecia areata. Clinical and Experimental Dermatology: Clinical dermatology. 2002; 27(5):405-9. <https://doi.org/10.1046/j.1365-2230.2002.01077.x> PMID:12190641
  6. Alzolibani AA. Epidemiologic and genetic characteristics of alopecia areata (part 1). Acta Dermatoven APA. 2011; 20(4):191-8.
  7. Alzolibani AA, Zari S, et al. Epidemiologic and genetic characteristics of alopecia areata (part 2). Acta Dermatovenerol Alp Pannonica Adriat. 2012; 21(1):15-19.
  8. Yang S, Yang J, Liu JB, Wang HY, Yang Q, Gao M, Liang YH, Lin GS, Lin D, Hu XL, Fan L. The genetic epidemiology of alopecia areata in China. British Journal of Dermatology. 2004; 151(1):16-23. <https://doi.org/10.1111/j.1365-2133.2004.05915.x> PMID:15270868
  9. Xiao FL, Yang S, Liu JB, He PP, Yang J, Cui Y, Yan KL, Gao M, Liang YH, Zhang XJ. The epidemiology of childhood alopecia areata in China: a study of 226 patients. Pediatric dermatology. 2006; 23(1):13-8. <https://doi.org/10.1111/j.1525-1470.2006.00161.x> PMID:16445403
  10. Unger WP. Systemic corticosteroids in alopecia totalis. Canadian Medical Association Journal. 1973; 108(2):177-180. PMID:4684625 PMCID:PMC1941146
  11. Tosti A, Guidetti MS, Bardazzi F, Misciali C. Long-term results of topical immunotherapy in children with alopecia totalis or alopecia universalis. Journal of the American Academy of Dermatology. 1996; 35(2):199-201. [https://doi.org/10.1016/S0190-9622\(96\)90323-0](https://doi.org/10.1016/S0190-9622(96)90323-0)
  12. Bajaj DR, Devrajani BR, Shah SZ, Ghauri RA, Matlani BL. Treatment of extensive alopecia areata with oral prednisolone mini-pulse regimen. Journal of Pakistan Association of Dermatology. 2016; 18(4):226-31.
  13. Harries MJ, Sun J, et al. Management of alopecia areata. Bmj. 2010; 341(1):c3671-c3671. <https://doi.org/10.1136/bmj.c3671> PMID:20656774 PMCID:PMC3230136
  14. Michalowski R. Alopecia areata totalis/universalis and systemic corticosteroids. International journal of dermatology. 1999; 38(12):947. PMID:10671096
  15. MacDonald Hull SP, Wood ML, Hutchinson PE, Sladden M, Messenger AG. Guidelines for the management of alopecia areata. British Journal of Dermatology. 2003; 149(4):692-9. <https://doi.org/10.1046/j.1365-2133.2003.05535.x> PMID:14616359
  16. Zargari O, Hejazi S, Shahidi-Dadras M, Younespour S, Robati R, Firooz A, Toosi P, Feldman SR. Considerable variation among Iranian dermatologists in the dosing and monitoring of methotrexate for treating psoriasis. International journal of dermatology. 2014; 53(3):385-9. <https://doi.org/10.1111/ijd.12201> PMID:24134730
  17. Joly P. The use of methotrexate alone or in combination with low doses of oral corticosteroids in the treatment of alopecia totalis or universalis. Journal of the American Academy of Dermatology. 2006; 55(4):632-6. <https://doi.org/10.1016/j.jaad.2005.09.010> PMID:17010743
  18. Chartaux E, Joly P. 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. In Annales de dermatologie et de venerologie. 2010; 137(8-9):507-513.
  19. Royer M, Bodemer C, Vabres P, Pajot C, Barbarot S, Paul C, Mazereeuw J. Efficacy and tolerability of methotrexate in severe childhood alopecia areata. British Journal of Dermatology. 2011; 165(2):407-10. <https://doi.org/10.1111/j.1365-2133.2011.10383.x> PMID:21517797
  20. Firooz AR, Fouladi DF. Methotrexate Plus Prednisolone in Severe Alopecia Areata. American Journal of Drug Discovery and Development. 2013; 3: 188-193. <https://doi.org/10.3923/ajdd.2013.188.193>
  21. Tosti A, Piraccini BM, Pazzaglia M, Vincenzi C. Clobetasol propionate 0.05% under occlusion in the treatment of alopecia totalis/universalis. Journal of the American Academy of Dermatology. 2003; 49(1):96-8. <https://doi.org/10.1067/mjd.2003.423> PMID:12833016
  22. Choi HJ, Ihm CW. Acute alopecia totalis. Acta Dermatovenerol Alp Pannonica Adriat. 2006; 15(1):27-34.
  23. Shaheedi-Dadras M, Karami A, Mollaei F, Moravvej H, Malekzad F. The effect of methylprednisolone pulse-therapy plus oral cyclosporine in the treatment of alopecia totalis and universalis. Arch Iran Med. 2008; 11(1):90-3. PMID:18154427
  24. Droitcourt C, Milpied B, Ezzedine K, Hubiche T, Belin E, Akpadjan F, Taïeb A, Seneschal J. Interest of high-dose pulse corticosteroid therapy combined with methotrexate for severe alopecia areata: a retrospective case series. Dermatology. 2012; 224(4):369-73. <https://doi.org/10.1159/000339341> PMID:22738995
  25. Alsantali A. Alopecia areata: a new treatment plan. Clinical, cosmetic and investigational dermatology. 2011; 4:107. <https://doi.org/10.2147/CCID.S22767> PMID:21833161 PMCID:PMC3149478
  26. Garg S, Messenger AG. Alopecia areata: evidence-based treatments. 2009; 28(1):15-8.
  27. Farshi S, Mansouri P, Safar F, Khiabanloo SR. Could azathioprine be considered as a therapeutic alternative in the treatment of alopecia areata? A pilot study. International journal of dermatology. 2010; 49(10):1188-93. <https://doi.org/10.1111/j.1365-4632.2010.04576.x> PMID:20883409
  28. Gianfaldoni S, Tchernev G, Wollina U, Lotti T. A Case of Alopecia Areata in a Patient with Turner Syndrome. Open Access Maced J Med Sci. 2017; 5(4):493-496. <https://doi.org/10.3889/oamjms.2017.127> PMID:28785342 PMCID:PMC5535667