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Research Article

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Efficacy and Safety of Low-Dose Methotrexate in Pediatric Refractory *Alopecia Areata*: A Retrospective Case Series

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ABSTRACT

Alopecia areata (AA) is a chronic autoimmune disorder causing non-scarring hair loss, with a significant psychosocial impact, particularly in pediatric patients with severe, refractory forms. While various treatments exist, effective and well-tolerated options for this population remain a clinical challenge. This study aimed to evaluate the safety and effectiveness of low-dose methotrexate (MTX) in pediatric patients with refractory AA.

This retrospective case series included 24 pediatric patients (11 males, 13 females; mean age 9.1 ± 4.5 years) with severe refractory AA. Patients received oral MTX (0.4 mg/kg weekly, with folic acid supplementation), 9 children were given dexamethasone 0.1mg in mini oral pulse at the Dermatology Department of Tripoli Central Hospital and a private clinic from December 2021 to January 2024. Hair regrowth was categorized as good (>75% regrowth), moderate (50-75% regrowth), little (<50% regrowth), or no response. Recurrence rates and adverse effects, including liver enzyme levels, were documented.

Of the 24 patients, 5 missed follow-up appointments. Among the 19 patients who completed treatment and follow-up, 16 (84.2%) experienced good to moderate hair regrowth. The recurrence rate among the 19 patients who completed follow-up was 31.6% (6 patients). Minimal adverse effects were observed, with only one patient showing a mild increase in aspartate transaminase (AST) levels. The study population included various forms of alopecia, with 41.7% having AA and 58.3% having *Alopecia universalis* (AU). Associated conditions included low ferritin levels (25%) and hypothyroidism (12.5%).

Low-dose methotrexate appears to be a generally effective and well-tolerated treatment option for pediatric patients with severe refractory *Alopecia areata*. These findings suggest MTX can induce significant hair regrowth with a low incidence of adverse events. Further research with larger sample sizes, standardized outcome measures, and longer follow-up periods, ideally in prospective studies with control groups, is warranted to confirm these results and explore long-term outcomes.

Keywords- *Alopecia areata; Methotrexate; Pediatric; Refractory; Autoimmune; Hair loss.*

INTRODUCTION

*Alopecia areata (*AA) is a chronic autoimmune disorder characterized by non-scarring hair loss due to immune-mediated attack on hair follicles. While many cases are self-limiting, relapses are common, and severe forms can significantly impact quality of life.[1] The global prevalence of AA is approximately 2%, with a higher incidence reported in children (1.92%) compared to adults (1.47%).[2] Genetic predisposition is suggested by familial cases and associations with conditions like Down syndrome and Turner syndrome, indicating a complex polygenic etiology.[3]

Pediatric patients with severe AA often face a worse prognosis than adults and are particularly vulnerable to psychosocial consequences, making effective treatment crucial.[4] Diagnostic approaches typically involve clinical examination, often supplemented by trichoscopy, with additional tests like Wood's light or skin scraping to rule out *Tinea capitis*. Blood tests may be considered to investigate suspected autoimmune comorbidities, such as celiac disease.

Current treatment options for pediatric AA include short-term systemic corticosteroids for acute, rapidly progressive disease, and various topical therapies such as minoxidil, dithranol, calcineurin inhibitors, and immunotherapy (e.g., diphenylcyclopropenone). Newer agents, such as Janus kinase (JAK) inhibitors (e.g., tofacitinib, baricitinib, ritlecitinib), have shown promise, with baricitinib receiving FDA approval for use in patients over 12 years of age.[5] Clinical trials have demonstrated significant hair regrowth in a substantial proportion of adult and adolescent patients treated with ritlecitinib.

Given the unpredictable course of AA, the high relapse rate even after successful regrowth and the association of young age at presentation with poor prognosis, there is a clear need for safe and effective long-term treatment strategies for pediatric refractory AA. While methotrexate has shown promise, there is limited data on its efficacy and safety specifically within the Libyan pediatric population. This retrospective case series aims to evaluate the outcomes of low-dose methotrexate treatment in children

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with refractory *Alopecia areata* at our centers, thereby contributing to the understanding of methotrexate's role in this challenging patient population.

MATERIALS AND METHODS

Study Design and Setting

This was a retrospective case series evaluating the safety and effectiveness of oral methotrexate (MTX) in pediatric patients with severe refractory *Alopecia areata* (AA). The study was conducted at the Dermatology Department of Tripoli Central Hospital and a private clinic in Libya, covering the period from December 2021 to January 2024.

Ethical Approval

This work was approved by the ethical committee of the Faculty of Medicine, University of Tripoli.

Participants

The study included pediatric patients diagnosed with severe refractory AA who were treated with MTX. A total of 24 patients were analyzed, comprising 11 males (45.8%) and 13 females (54.2%). The mean age of participants was 9.125 years, with a standard deviation of ± 4.5 years. Patients were included if they had severe AA refractory to conventional treatments and were aged 18 years or younger at the time of MTX initiation. Severe AA was defined as >50% scalp involvement. Refractory AA was defined as failure to respond to at least two previous treatment modalities, including high-potency topical steroids and topical immunotherapy, applied for a minimum of 6 months. Exclusion criteria included known contraindications to MTX or incomplete medical records.

Data Collection

Data were retrospectively collected from existing medical records. Information gathered included demographic details (age, gender), specific diagnosis of alopecia (AA multiple patches, *Alopecia universalis*, and *ophiasis*), duration of alopecia, family history of autoimmune diseases, treatment details (MTX dosage, duration, concomitant therapies), and follow-up results. Patients were assessed for hair regrowth outcomes, categorized as follows:

- *Good response*: >75% terminal hair regrowth
- *Moderate response*: 50-75% terminal hair regrowth
- *Little response*: <50% terminal hair regrowth
- *No response*: No change or worsening of hair loss

Recurrence rates and any adverse effects related to MTX treatment, such as liver enzyme levels (specifically aspartate transaminase, AST), were also documented.

Treatment Protocol

Patients received oral methotrexate at an initial dosage of 0.4 mg/kg once per week, starting with a 2.5 mg tablet and subsequently adjusted based on body weight and clinical response, adhering to established clinical guidelines for pediatric MTX use. The maximum weekly dose did not exceed 20mg. Dose increases were made based on clinical response and tolerability. Folic acid supplements (5 mg) were administered daily, except on the day of MTX administration, to mitigate potential side effects. Routine lab monitoring, including complete blood count and liver function tests, was performed at baseline, one month, and every three months thereafter. Treatment duration varied based on individual patient responses and clinical judgment, ranging from 3 months to 1 year.

Outcome Measures

The primary outcome measure was the percentage of patients achieving good to moderate hair regrowth. Secondary outcomes included the recurrence rate of AA and the incidence of adverse effects related to MTX treatment, particularly elevated liver enzyme levels.

Statistical Analysis

Descriptive statistics were used to summarize patient demographics and treatment outcomes. Continuous variables were presented as means ± standard deviation, and categorical variables as counts and percentages. The data were analyzed to determine the overall effectiveness and safety profile of MTX, with a focus on response rates and the occurrence of adverse events.

RESULTS

This study included 24 pediatric patients diagnosed with various forms of alopecia. The cohort comprised 11 males (45.8%) and 13 females (54.2%). The mean age of participants was 9.1 ± 4.5 years.

Baseline Characteristics and Alopecia Types

Patients presented with diverse forms of alopecia. The most common diagnosis was *Alopecia universalis* (AU) in 14 patients (58.3%), followed by *Alopecia areata* (AA) in 10 patients (41.7%). Of these, 3 patients presented with an ophiasis pattern (Figure 1).

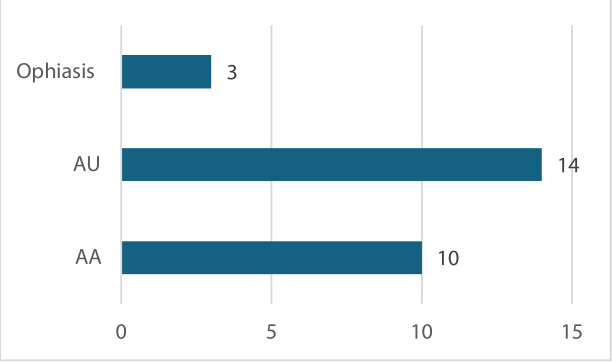


Figure 1: The count of clinical presentation of participants

Notably, while most patients reported no associated illnesses, 6 patients (25%) had low ferritin levels, and 3 patients (12.5%) were diagnosed with hypothyroidism. The

duration of *Alopecia* among participants varied significantly, ranging from 3 months to 6 years, with approximately 75% of patients presenting for treatment more than one year after disease onset. A family history of autoimmune diseases, including bronchial asthma, *Alopecia areata*, *Alopecia universalis*, hypothyroidism, vitiligo, and rheumatoid arthritis, was reported by 12 participants (50%) (Figure 2).

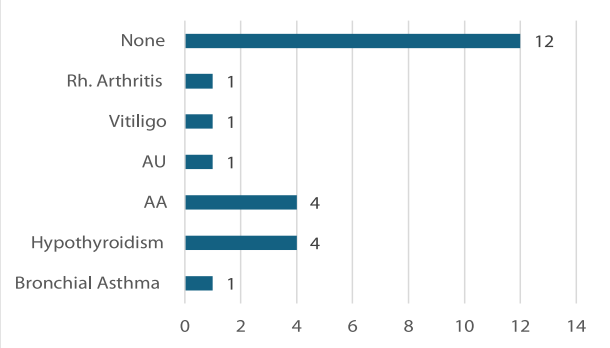


Figure 2: Count of family history of autoimmune diseases.

Treatment Response and Recurrence

The duration of methotrexate treatment ranged from 3 months to 1 year. A positive correlation was observed between treatment duration and efficacy, with the highest response rates noted in courses lasting more than 6 months. Concomitant treatments, tailored to individual patient conditions, age, and associated deficiencies, included dietary supplements (zinc, ferrous sulfate, folic acid, multivitamins), squaric acid dibutyl ester (SADBE), dexamethasone pulse therapy, topical steroids, and minoxidil 2%.

Out of the 24 patients, 5 missed follow-up appointments. Among the 19 patients who completed the treatment and follow-up, 16 (84.2%) experienced good to moderate hair growth. Among these 19 patients, 6 (31.6%) experienced a recurrence of the disease, consisting of 3 males and 3 females (Figure 3).

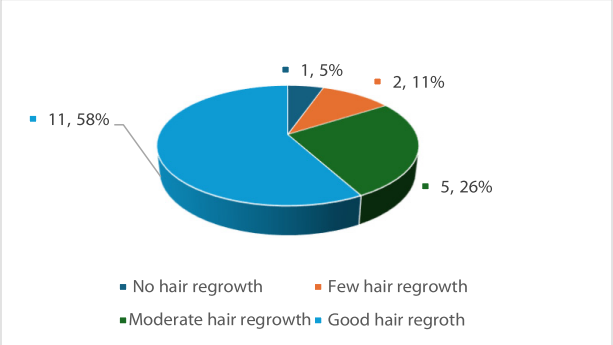
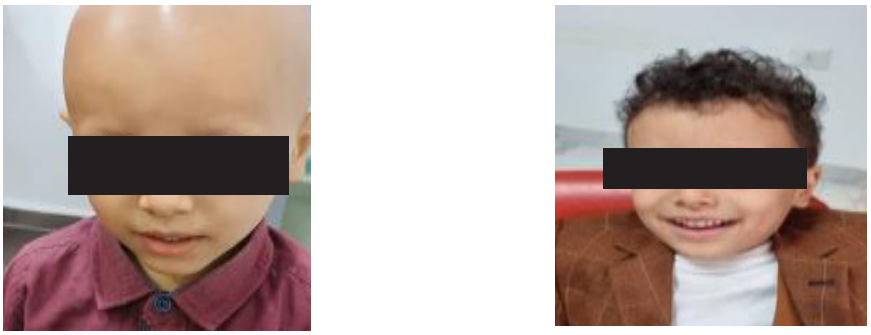


Figure 3: Response to MTX treatment



A B

Picture 1: Clinical response to methotrexate in a 4-year-old male with alopecia universalis. (A) At baseline, showing complete loss of scalp hair. (B) After one year of treatment, showing significant terminal hair regrowth across the scalp.

A B

Picture 2: Clinical response to methotrexate in a 5-year-old female with *Alopecia universalis* and hypothyroidism (A) At baseline, showing complete loss of scalp hair. (B) After one year of treatment, showing significant terminal hair regrowth scalp, eyebrows and eyelashes.

Adverse Effects

Adverse effects related to methotrexate treatment were minimal. Only one patient exhibited a mild elevation in aspartate transaminase (AST) levels, indicating good overall tolerability of the treatment in this pediatric cohort.

DISCUSSION

This retrospective case series provides valuable insights into the efficacy and safety of low-dose methotrexate for pediatric patients with severe refractory *Alopecia areata*. The findings suggest that MTX can be an effective therapeutic option, with 84.2% of those who completed follow-up achieving good to moderate hair regrowth. This outcome is particularly significant given the challenging nature of refractory AA in children and the limited availability of robust therapeutic options.[4] The observed efficacy aligns with previous systematic reviews and meta-analyses supporting MTX use in both pediatric and adult AA.[6,7] For instance, Phan et al. (2019) reported a pooled response rate of 60% for MTX in AA, suggesting our findings are comparable, if not slightly higher, possibly due to patient selection or concomitant therapies.[6]

The patient demographic, with a mean age of 9.125 years and a slight female predominance, underscores the profound psychosocial implications of AA in this young population. The high prevalence of *Alopecia universalis* (58.3%) within our cohort highlights the need for potent immunosuppressive therapies, as AU is typically one of the most difficult forms of AA to manage.[2]

The study noted a low incidence of adverse effects, with only one patient experiencing a mild increase in AST levels. This favorable safety profile is crucial for pediatric patients, where long-term medication safety is a primary concern. The use of folic acid supplementation likely contributed to the low toxicity observed, consistent with standard MTX protocols.[6] This finding supports MTX as a relatively safe option when administered judiciously and monitored appropriately.

Furthermore, the presence of associated health issues such as low ferritin levels and hypothyroidism in a subset of patients emphasizes the importance of a comprehensive pre-treatment evaluation. These comorbidities may influence disease severity and treatment response, suggesting that addressing underlying conditions could enhance MTX efficacy and overall patient outcomes. The concurrent use of dietary supplements and other topical or systemic therapies reflects a holistic management approach, which may synergistically improve treatment effectiveness by addressing potential nutritional deficiencies or localized disease activity.

Limitations

This study has several limitations that warrant consideration. As a retrospective case series, it inherently introduces potential biases, such as selection bias and recall bias, and limits the ability to establish definitive causality. The relatively small sample size of 24 patients restricts the generalizability of the findings and the statistical power to detect less common adverse events or subtle treatment differences. The lack of a control group also prevents direct comparison of MTX efficacy against placebo or other active treatments, making it difficult to definitively attribute all observed improvements solely to methotrexate, especially given the variable concomitant treatments used. Specifically, the concurrent use of oral mini-pulse dexamethasone in 9 of the 24 patients is a significant confounding factor that may have contributed to the high observed response rate, making it difficult to attribute the success solely to methotrexate. Furthermore, the categorization of hair regrowth, while clinically relevant, lacks a standardized, objective scoring system, which could introduce subjectivity. Finally, the duration of follow-up, ranging from 3 months to 1 year, may be insufficient to assess the long-term efficacy and recurrence rates of AA following MTX treatment.

CONCLUSION

This study demonstrates that low-dose methotrexate is a generally effective and well-tolerated treatment option for pediatric patients with severe refractory *Alopecia areata*. The observed rates of good to moderate hair regrowth, coupled with a low incidence of adverse effects, support its utility in this challenging patient population. These findings contribute to the growing evidence base for MTX in pediatric AA. Future research should focus on prospective, randomized controlled trials with larger cohorts, standardized outcome measures, and extended follow-up periods to further elucidate the long-term efficacy, safety, and optimal dosing strategies of methotrexate in pediatric *Alopecia areata*.

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