The Effect of Mehotrexate in the Treatment of Alopecia Areata

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ABSTRACT

Background: Alopecia areata (AA) is one of the most common autoimmune disorders and its severe types are resistant to almost all conventional therapies. Methotrexate (MTX) has been used as an adjunctive therapy in some autoimmune disorders and has been proposed to be effective in the treatment of severe alopecia areata both as a monotherapy and in combination with corticosteroids.

Aim of the study: was to evaluate the outcome and safety of MTX therapy in patients with severe forms of AA, whether as monotherapy or in combination with systemic or intralesional corticosteroids; and to assess therapeutic response according to sex, age, pattern of AA, disease duration and cumulative MTX dose.

Methods: 28 patients were evaluated in a retrospective, non-controlled study, with alopecia areata in current or prior treatment with methotrexate to assess the therapeutic response according to sex, age, pattern of alopecia areata, disease duration, and cumulative dose of methotrexate as well as the use of systemic corticosteroids or other treatments, and drug safety.

Results: 77.8% % of patients experienced a more than 50% regrowth rate, with the best responses observed in those with <5 years of disease progression (81%), age over 40 years (84.6%), male patients (80%), cumulative dose of methotrexate 1000-1500 mg, and multifocal alopecia areata (83.3%), patients receiving systemic corticosteroids in combination with methotrexate, 78.5% had greater than 50% regrowth, compared with 45.3% in those who used methotrexate alone. The therapeutic dose ranged from 10-25 mg/week. No patient had serious adverse effects. Relapse was observed in 35.4% of patients with more than 50% regrowth

Conclusion: methotrexate is a convenient and relatively inexpensive drug that could be used as a safe and well tolerated adjunctive therapy for severe alopecia areata although careful monitoring of adverse effect is necessary.

Keywords: alopecia areata, methotrexate, severe alopecia areata.

INTRODUCTION

Alopecia areata is a non-scarring chronic inflammatory disease that affects the hair follicle and sometimes the nail. The onset may be at any age and there is no known race or sex preponderance [1].

Alopecia areata (AA) is a common cause of non scarring alopecia that occurs in a patchy, confluent or diffuse pattern. It may involve loss of hair from some or all areas of the body, usually from the scalp [2]. In 1–2% of cases, the condition can spread to the entire scalp (Alopecia totalis) or to the entire epidermis (Alopecia universalis). AA has a reported incidence of 0.1–0.2% with a lifetime risk of 1.7% with men and women being affected equally [3].

Depending on the number and distribution of lesions and the extent of involvement, it is classified clinically into the following patterns: unifocal, multifocal, ophiasis, totalis, universalis, sisaipho (or ophiasis inversus), reticular, and diffuse[4].

Potential autoimmune mechanisms involved in the pathogenesis of AA include sensitization of T lymphocytes, particularly CD8+ T cells, to follicular antigens[5].Activation of the lymphocytes that compose the perifollicular infiltrate characteristic of AA induces release of several Th1 cytokines - interleukin (IL)-1 alpha, IL-1 beta, and tumor necrosis factor (TNF) alpha - capable of inhibiting hair follicle growth and arresting hair synthesis, with early termination of anagen[6].

Several treatment options have been suggested for AA, but there is a paucity of randomized, doubleblind, placebo-controlled trials, and, as noted above, no therapy is able to modify the course of the disease[7].

Treatment of severe AA with conventional therapies such as topical corticosteroids (CS), topical immunotherapy, PUVA or intravenous (IV) pulse CS is usually disappointing; even newly introduced biological drugs such as anti-tumor necrosis factor drugs (infliximab and

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etanercept) and anti-CD11a (efalizumab) have been ineffective [8,9].

Methotrexate (MTX) is an effective drug in the treatment of some cases of severe and chronic eczema, refractory late-onset atopic dermatitis, psoriasis and bullous pemphigoid and is an effective and well tolerated therapy in severe AA, either as a single therapy or in combination with CS[10]. In addition, MTX can be used as CS sparing agent in many autoimmune disorders such as bullous pemphigoid and pemphigus vulgaris [11]. Systemic corticosteroids have been used in the treatment of AA since the 1950s but there is concern over the side effects of long-term treatment with high doses of CS[12]. However, over the past years, a variety of therapy regimens with high doses of CS has been introduced including different CS pulse regimens, alternating daily dose and monthly dose of CS in order to reduce systemic side[13].

This study evaluates the utilization of MTX as a treatment modality in patients with alopecia areata effects of CS 17-22.

PATIENTS AND METHODS

The present retrospective study evaluated 28 patients with AA presented at King Abdulaziz Hospital.

Inclusion criteria

The sample comprised:

1. Patients with extensive forms of AA (multifocal, universalis, totalis, and diffuse) refractory to previous treatment attempts,
2. Patients over 15 years of age.
3. Absence of hepatic impairment (confirmed by laboratory testing).
4. Absence of active tuberculosis infection (confirmed by clinical examination or PPD and chest X-ray).
5. Absence of pregnancy, and COCP (combined oral contraceptive) use. Furthermore, patients were informed of possible side effects and MTX was only prescribed after patient consent had been obtained.

We evaluated the following parameters: disease duration, concomitant therapies (including systemic corticosteroid therapy), pattern of alopecia, weekly MTX dose, cumulative dose of MTX in mg (stratified into predetermined ranges: <500 mg; 501-1000 mg; 1001-1500 mg; 1501-2000 mg; 2001-2500 mg; and >2500 mg), hematologic and/or hepatic adverse events, treatment duration, and therapeutic response. Regrowth was stratified into five categories: 0-25%; 26-50%; 51-75%; 76-99%; and 100%. All patients underwent a comprehensive outpatient workup, which included a complete blood count and measurement of transaminase, creatinine, bilirubin, and gamma-glutamyl transpeptidase levels, at baseline, 1 month, and every 3 months thereafter during the follow-up period. In some patients, a chest X-ray, PPD skin testing, and a hepatitis serology panel were also performed before treatment. Patients who received a total cumulative dose of MTX >2 g underwent abdominal ultrasound and liver biopsy.

RESULTS

The median patient age was 39 years, and the median disease duration was 5 years (range, 0.4-42 years). Of the patients assessed, 64.2% were female and 35.7% were male. The most common pattern of AA was multifocal (50.0%), followed by universalis (32.14%), diffuse (10.71%), and totalis (7.14%), table 1.

Table 1: Key clinical and treatment-related characteristics of the sample

Case no	Type of Alopecia areata	Age/ Gender	Systemic cortico-steroid therapy	Total cumulative dose (mg)	% improvement
1	Diffuse	29/F	No	1-499	0%
2	Diffuse	26/F	Yes	500-999	25-50%
3	Diffuse	22/F	Yes	1500-1999	75-95%
4	Totalis	51/F	Yes	1000-1499	51-75%
5	Totalis	48/F	No	1-499	25-50%
6	Universalis	46/M	Yes	500-999	51-75%
7	Universalis	56/F	No	3000-3499	25-50%
8	Universalis	49/F	Yes	2500-2999	0%
9	Universalis	42/M	Yes	1000-1499	0%
10	Universalis	41/F	Yes	2000-2499	75-95%
11	Universalis	33/M	Yes	1500-1999	0%
12	Universalis	37/F	No	500-999	25-50%
13	Universalis	48/M	Yes	1-499	51-75%
14	Universalis	45/F	Yes	1-499	51-75%
15	Multifocal	34/F	No	1-499	25-50%
16	Multifocal	29/F	No	1000-1499	100%
17	Multifocal	39/M	No	1000-1499	75-95%
18	Multifocal	31/F	Yes	2000-2499	100%
19	Multifocal	35/M	Yes	1000-1499	100%
20	Multifocal	42/F	No	1500-1999	75-95%
21	Multifocal	36/F	Yes	1500-1999	100%
22	Multifocal	41/M	Yes	500-999	100%
23	Multifocal	36/M	Yes	500-999	75-95%
24	Multifocal	34/F	No	500-999	75-95%
25	Multifocal	42/M	Yes	500-999	51-75%
26	Multifocal	38/F	Yes	1-499	51-75%
27	Multifocal	35/F	Yes	1-499	100%
28	Multifocal	47/M	Yes	1000-1499	75-95%

The majority of patients had previously received trials of therapy, such as topical sensitizers (62%) and systemic corticosteroids (59.1%), either unsuccessfully or with disease recurrence after withdrawal of treatment.

The starting dose of MTX ranged from 10 to 25 mg (±15 mg), as did the median therapeutic dose (±20 mg). The cumulative dose to onset of response ranged from 30 to 630 mg (±180 mg). The distribution of cumulative doses in the sample was as follows: <500 mg, 25.0%; 500-1000 mg, 25%; 1000-1500 mg, 21.4%; 1500-2000 mg, 14.3%; and >2000 mg, 10.7%.

A therapeutic response with regrowth over >50% of the scalp was observed in 67.9% (n=19) of all patients, with 25% (n=7) achieving 75-95% regrowth and 19.3% (n=6) achieving 100% regrowth. The frequency of regrowth was significantly greater among men (80%, $p>0.05$), patients aged 40 years or older (84.6%, $p>0.05$), and those taking a cumulative MTX dose of 1000-1500 mg (83.3%, $p>0.05$).

Moreover, it has also been observed that superior responses were observed in patients with a disease duration <5 years (81% regrowth), with the overall regrowth rate dropping to 48.7% in patients with disease duration >5 years. There was a significant inverse association between disease duration and percent improvement ($p=0.02$); an inversely proportional trend was notices; the shorter the disease duration, the greater the improvement. Regarding AA patterns, >50% regrowth was observed in 94.9% with multifocal, 44.4% with universalis, 50% with totalis, and 33.3% with diffuse AA. The difference between the two most prevalent forms, universalis and multifocal, was significant ($p=0.018$).

Table 2: Distribution of regrowth in the different types of alopecia areata represented in the sample, stratified by prevalence

AA type		Totalis	Multifocal	Universalis	Diffuse
Sample-wide prevalence (%)	**%**	7.1	50.0	32.1	10.7
	N	**2**	14	9	3
> 50% regrowth	**%**	**50.0**	**92.9**	**44.4**	**33.3**
	N	**1**	13	4	1

The treatments combined with MTX included topical minoxidil, intralesional corticosteroids, and systemic corticosteroids (prednisone). Only one patient did not use any combination therapy. The most common combination therapy added to MTX was topical minoxidil + systemic corticosteroid (34%).

Among the patients who used systemic corticosteroids in combination with MTX (70%), 77.8% experienced >50% regrowth. Most used steroids only during the first months of treatment. Among those who did not use systemic corticosteroids in combination with MTX (30%), only 45.3% experienced >50% regrowth. There was no significant association between corticosteroid therapy and treatment response. The duration of combination corticosteroid therapy ranged from 1 to 12 months (±4 months), and the dose, from 20 to 30 mg/day (±30 mg).

All patients underwent complete blood count and liver and kidney function tests at baseline. Nine also underwent hepatitis serologies (all non-reagent) and nine underwent PPD testing, of whom three were strongly reactive, despite normal chest X-ray.

All patients received folic acid supplementation (5 mg) at least once weekly, on the day after MTX. Folic acid administration was increased to three weekly doses in patients with MTX intolerance or gastric or hematologic adverse effects.

Regarding treatment tolerance, only three patients (9.3%) reported gastrointestinal side effects (nausea, epigastric pain, and diarrhea), which were managed by scaling up folic acid supplementation and dividing the MTX dose, with improvement of symptoms in two patients; only one required treatment discontinuation.

Hematologic adverse effects (mild to moderate leucopenia, without clinical significance) were observed in 9.7% (n=3) of patients, and improved after folic acid supplementation was increased.

Hepatic adverse effects (mild, transient increase in transaminases) were observed in 6.5% (n=2) of patients, one of whom had alcoholism. Abdominal ultrasound and liver biopsy, performed in three patients with a cumulative MTX dose of >2 g (9.6% of patients), were within normal limits.

The duration of follow-up ranged from 3 to 51 months (±13). Relapse occurred in 33.3% (n=7) of patients with >50% regrowth (n=21) and in 40% (n=6) of patients with >75% regrowth (n=15). The pattern of alopecia at relapse was multifocal (small plaques) in six patients and AA totalis in one patient. Options for relapse management included initiation of prednisone, increase in MTX dosage, intralesional corticosteroids, or topical dithranol.

DISCUSSION

Since alopecia areata is believed to be an autoimmune condition, different immunomodulators have been used to treat this condition. Several therapeutic options are available for the treatment of extensive or refractory AA.

These include intralesional, topical, or systemic corticosteroids; minoxidil; dithranol; topical sensitizers (DNCB, DPCP); and PUVA. However, none of these modalities has proven curative or preventative action[14].

Methotrexate is ‘a folic acid antagonist and is classified as an antimetabolite cytotoxic agent[15]. potentially the reason why it is being studied in relation to aggressive Alopecia Areata – methotrexate has also been used to treat cases of severe, uncontrolled psoriasis which has not responded to other forms of therapy. Psoriasis is another autoimmune disorder but one which affects the skin rather than the hair follicles. In these instances, the drug is usually prescribed as an oral tablet in doses of 10-25mg, which In our sample, the mean therapeutic dose of MTX was approximately 15 mg and the dose required for onset of regrowth was 180 mg, i.e., onset of response took approximately 9 weeks.

MTX is known to inhibit the enzyme dihydrofolate reductase, which leads to a decrease in intracellular reduced folate concentrations. This decrease inhibits purine and pyrimidine metabolism and, consequently, nucleic acid synthesis, thus resulting in antineoplastic effects when administered at high doses[16] .MTX polyglutamates also inhibit AICAR (5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase), an enzyme involved in purine synthesis, which ultimately leads to a buildup of adenosine, a mediator of many of the anti-inflammatory effects of MTX. Adenosine is released into the extracellular space and, among multiple anti-inflammatory actions, inhibits white blood cell accumulation, leads to a reduction in TNF-α and IFN-γ synthesis, and inhibits a variety of monocyte, macrophage, and T-cell activities[17] . This action might explain the effect of MTX in AA.

In the present study, MTX was used in severe forms of AA (multifocal, universalis, totalis, and diffuse) to good effect (>50% regrowth in 67.7% of cases), with few adverse effects. These results are similar to those reported in a study by Droitcourt *et al*. [18] which reported satisfactory regrowth in 64% and 70% of patients respectively[18]. A study conducted in children also found no serious side effects, with >50% regrowth in five of 13 patients assessed[19].

Side effects of MTX

The main short-term adverse effects are hematologic, particularly pancytopenia. Other adverse effects include mucositis, oral and/or gastrointestinal ulcers, rash, photosensitivity, acne, alopecia, anorexia, diarrhea, nausea, and interstitial pneumonitis, particularly in patients with hypoalbuminemia. Long-term adverse effects are mostly hepatic, and may range from elevated transaminases to steatosis and cirrhosis Other long-term effects include pulmonary fibrosis, malignancy (increased risk of lymphoma in patients with psoriasis or rheumatoid arthritis), and increased risk of occlusive vascular disease (due to increased homocysteine levels) [20].

Based on the folate-depleting mechanism of action (both therapeutic and toxic) of MTX, studies have been conducted to assess the effect of folic acid or folinic acid supplementation given after MTX doses; all have demonstrated a reduction in adverse effects without loss of efficacy[21]. In the present study, folic acid was administered at a dose of 5 mg once to three times weekly.

Myelosuppression is one of the most fearsome adverse effects of MTX, due to both its severity and its unpredictability. Mild to moderate leukopenia (the most common manifestation), thrombocytopenia, and megaloblastic anemia occur in 3-24% of patients[20].

In our sample, three patients (9.7%) developed mild to moderate leukopenia, with improvement after increasing folic acid supplementation.

The risk of hepatotoxicity is increased in the presence of excess alcohol intake, concomitant retinoid therapy, diabetes mellitus, or obesity[22]. In the present study, two patients developed increased transaminases: one with a history of alcoholism (a known risk factor) and one on concomitant nonsteroidal anti-inflammatory drug therapy, which may increase plasma levels of MTX [23].

The use of systemic corticosteroids in combination with MTX

In the early months of treatment may mask therapeutic response. Nevertheless, it was associated with improved response, as in previous studies, although the difference was not significant in the present sample.

Joly (2010) and Droitcourt (2012) reported similar times to response onset: 2.5 and 3 months respectively[18,24]. Most patients with >50% regrowth received cumulative doses in the 1000-1500 mg range (87%), which suggests that these dose levels must be achieved before therapeutic response can be assessed.

A previous study found an 80% relapse rate in MTX-treated patients who experienced regrowth [24]. In our sample, relapse occurred in 33.3% (n=7) of patients with >50% regrowth (n=21), and in 20% of patients with >75% regrowth. One patient developed relapse during treatment, three at the time of treatment withdrawal (after dose reduction to <7.5 mg/week), and three a mean 6.3 months after MTX discontinuation, which suggests that an MTX dose of 7.5 mg/week is a good level to define the timing of drug discontinuation or the minimum effective dose for maintenance of remission.

LIMITATIONS OF THE STUDY

The present study is retrospective and non-comparative, hence, these results are limited by the study's retrospective nature. Also since patients recruited from a public hospital, there was a significant heterogeneous nature of subjects, as well as Larger samples studied in a blind, randomized fashion are required to

declare MTX as one option for a first-line therapy for AA.

Furthermore, the use of biomarkers currently in development for patient monitoring may encourage long-term use of MTX without requiring patients to undergo invasive testing.

CONCLUSION

Methotrexate is a relatively inexpensive and safe therapy to consider for patients with alopecia areata that does not respond to topical and/or intralesional corticosteroids or other local therapies. The present study has provided evidence that dose of 20 mg/week can be a safe and promising option for the treatment of severe forms of AA. The onset of response required a cumulative dose of 180 mg, and total cumulative doses of 1000-1500 mg were associated with the best results. Meanwhile, long-term maintenance treatment is usually required to maintain hair growth. Risks versus benefits must be carefully weighed.

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