Efficacy and safety of oral mega pulse methylprednisolone for severe therapy resistant *Alopecia areata*

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ABSTRACT

الأهداف: تقييم مدى فعالية استخدام الكورتيكوستيرويد الفموي بنظام مكثف بالطريقة النبضية بجرعات أعلى وأكثر تكراراً وذلك في معالجة الأنواع الوخيمة من الحاصة البقعية.

الطريقة: أُجريت هذه الدراسة الاستطلاعية العشوائية في قسم الأمراض الجلدية، مستشفى الملك خالد الجامعي، الرياض، المملكة العربية السعودية وذلك خلال الفترة من يناير 2003م إلى ديسمبر 2009م. لقد تم توزيع المرضى المصابين بحاصة بقعية شاملة وكلية وثعبانية الشكل على ثلاث مجموعات بشكل عشوائي. حيث تلقت المجموعة أ المعالجة بدواء الميثايل بريدنيزولون بطريقة نبضية ضخمة عن طريق الفم خلال 3 أيام متتالية مرة واحدة كل أسبوعين لمدة 24 أسبوع. بينما تلقت المجموعة ب العلاج نفسه خلال يومين متتاليين مرة واحدة كل 3 أسابيع. أما المجموعة ج فتلقت العلاج نفسه خلال 3 أيام متتالية كل 3 أسابيع. ولقد تمت مواصلة العلاج للمرضى الذين ظهر لديهم إعادة نمو للشعر بنسبة 75% أو أكثر في الأسابيع 24 أو 36 مع زيادة الفترات بين المعالجات النبضية تدريجياً.

النتائج: شملت الدراسة 42 مريض، وقد كان 52.4% من المرضى مصاباً بالأهبة الأتوبية، بينما كان 35.7% منهم مصاب بالتهاب الدرقية الناجم عن المناعة الذاتية. وأشارت نتائج الدراسة إلى إصابة 32 بالحاصة الشاملة، و4 بالحاصة الكلية، و6 بالحاصة الثعبانية الشكل. وبعد مرور 36 أسبوع من العلاج أظهر 12 مريض (28.6%) استجابة كافية، و9 (21.4%) استجابة غير كافية، و21 (50%) استجابة ضعيفة. ولم يكن اختلاف معدل الاستجابة بين المجموعات المختلفة ذي دلالة إحصائية. بينما ظهر هناك فروق ذات دلالات إحصائية واضحة في كل من التالي: عمر المصاب عند بداية المرض، ومدة المرض، ووجود انخفاض في وظائف الغدة الدرقية التحت السريرية وذلك في اختلاف الاستجابة بين المجموعات. وقد أظهر 13 مريض (38.2%) خلال فترة المتابعة انتكاساً في الحالة، وعانى 5 (14.7%) من المرضى من سقوط الشعر بشكل متوسط، و3 (8.8%) من سقوط شعر بشكل خفيف، بينما حافظ 7 مرضى (20.1%) على نمو الشعر لديهم، بالإضافة إلى ذلك فقد فقدنا متابعة 6 مرضى (17.6%). كما كان تحمل العلاج بهذه الطريقة جيداً للمجموعة ب وج.

خاتمة: يعد استخدام الميثيل بريدنيزولون بالطريقة النبضية الضخمة الفموية في معالجة الأنواع الوخيمة من داء الثعلبة خيار علاجي نسبي الفاعلية والتحمل ولكن يصاحبه نسبة انتكاس عالية وذلك في معالجة الأنواع الوخيمة من داء الثعلبة، مع العلم أن العديد من المرضى سيتعرضون لانتكاس بغض النظر عن استخدام المعالجة المحافظة.

Objectives: To use intensive regimen of pulse steroid in the severe forms of *Alopecia areata*.

Methods: This prospective randomized study was conducted at King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia between 2003 to 2009. Patients with *Alopecia universalis*, *Alopecia totalis,* or *Alopecia ophiasis* were assigned to one of the 3 treatment groups: Group A received oral mega pulse methylprednisolone (MP) for 3 consecutive days once every 2 weeks for 24 weeks; Group B received 2 consecutive daily pulses every 3 weeks; and Group C received 3 consecutive daily pulses every 3 weeks. Patients who showed regrowth of 75% or more at 24 or 36 weeks continued their treatment, while intervals were increased gradually.

Results: Forty-two patients were included in this study, and 52.4% of them had atopic diathesis, while 35.7% had autoimmune thyroiditis. At 36 weeks, 12 (28.6%) patients had adequate response, 9 (21.4%) had inadequate response, and 21 (50%) patients had poor response. The response rate shows no statistically significant difference between treatment groups. There were statistically significant differences in age of onset, duration of the disease, and presence of subclinical hypothyroidism between different response groups. At follow-up: 13 (38.2%) patients relapsed; 5 (14.7%) patients developed moderate hair fall; 3 (8.8%) patients developed mild hair fall; 7 (20.1%) patients maintained their hair regrowth; and 6 (17.6%) patients were lost follow up. It was relatively well-tolerated among groups B and C.

Conclusion: Oral mega pulse MP use in severe forms of *Alopecia areata* has relative efficacy and tolerance but with high relapse rate.

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Alopecia areata (*AA)* is a common cause of non-scarring alopecia with an estimated lifetime risk of 1.7% among the general population.[1] The treatment of AA continues to be difficult particularly for the severe forms of the disease such *Alopecia Totalis* (*AT*), *Alopecia Universalis* (*AU*) and *Ophiasic Alopecia* (*OA*). Several treatments may stimulate hair growth in *AA*, but none have been shown to modify the course of the disease.[2] Systemic glucocorticoids (GC) have been shown to be effective on the short-term- but carry the risks of severe side effects in long term therapy.[3] Interest in systemic corticosteroids was regenerated in 1975 by Barton and Shuster who used a single 2 gm IV methylprednisolone (MP) pulse in 22 patients with *AA* with little success.[4] Subsequent reports using different regimens have shown the effectiveness of pulse GC in widespread *AA* but not the *AT*, *AU,* or *OA* type.[2-6] Whether the failure is due to inadequate dosing, inadequate frequency, or other factors is a matter of debate. We decided to conduct this study using the same approach, however with the aim to assess the efficacy and safety of an intensive regimen using higher doses and more frequent pulses to patients with severe forms of *AA*.

Methods. Patients diagnosed with either *AU*, *AT,* or *OA* were included in this single-center, prospective, randomized study conducted at the Dermatology Department of King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia between January 2003 to December 2009. Patients with contraindications to steroid therapy were excluded. After exclusion, 42 eligible patients were randomly assigned to one of the 3 treatment groups. Enrolled patients provided written informed consent. Institutional review board approval was obtained. The study was conducted according to the principles of Helsinki Declaration. At visit 1 (week 0), patients were screened for eligibility. They provided a full medical history and underwent physical examination. The following laboratory tests were performed: electrocardiography, tuberculin test, thyroxine, thyroid-stimulation hormone and thyroid autoantibodies, antinuclear antibodies, IgE level, and ferritin level was carried out before treatment. Complete blood cell count, fasting blood sugar, sodium, potassium, chloride, urea, creatinine, calcium, alkaline phosphatase, bilirubin, alanine aminotransferase, aspartate aminotransferase, cholesterol, triglyceride, urinalysis was carried out before treatment, and every 12 weeks. Chest and sinus x-ray, and ophthalmologic examination were carried out before treatment and every 24 weeks. Short synacthen test was carried out before treatment, and one week after the first treatment cycle. Bone mineral density was measured by dual-energy x-ray absorptiometry (DEXA) scan before, and on last patients visit. Scalp biopsies was carried out before treatment in all patients, and also at the end of treatment in 16 patients. Weight, temperature, and blood pressure were measured at each visit. Electrocardiography and serum electrolytes were carried out also 2 hours after each drug administration. Patients were monitored for signs and symptoms of adverse events throughout study.

Pulse treatment and dosing protocols. Patients were randomly assigned to one of the 3 treatment groups. Group A (6 patients) received pulse treatment, each pulse course for 3 consecutive days once every 2 weeks for 24 weeks. We stopped enrolling patients in this group after 2 of our 6 patients developed extensive striae and one developed pneumonia. Group B (9 patients) received 2 consecutive daily pulses every 3 weeks for 24 weeks. No more patients were enrolled in this group due to the inadequate response observed after 8 sessions of treatment compared to Group A. Group C (27 patients) received 3 consecutive daily pulses every 3 weeks for 24 weeks. The oral dose of daily dose of MP sodium succinate 15 mg/kg of ideal body weight (IBW)/day, dissolved in 200 ml of fresh orange juice.[7]

Efficacy analysis. The efficacy analysis was based on photography analysis. The scalp photos were obtained at baseline and every 2 visits afterward. The evaluation was carried out by 2 blinded dermatologists. The main efficacy measure was the proportion of responders at 36 weeks. Efficacy was classified as adequate (≥75%) re-growth of terminal hair in the affected area, inadequate (25-74%), and poor if (<25%) regrowth of terminal hair. Mild hair fall was defined as fall of ≤25 % of regrowing hair. Moderate hair fall was defined as fall of >25% of regrowing hair. Relapse was defined as recurrence or worsening of alopecia from its original severity. First efficacy analysis was carried out after 24 weeks of treatment. If regrowth of terminal hair was less than 50% of the originally affected scalp, treatment was discontinued. If regrowth was observed between 50-75% of affected scalp, treatment was continued for 12 weeks more, then reassessed again. If the regrowth

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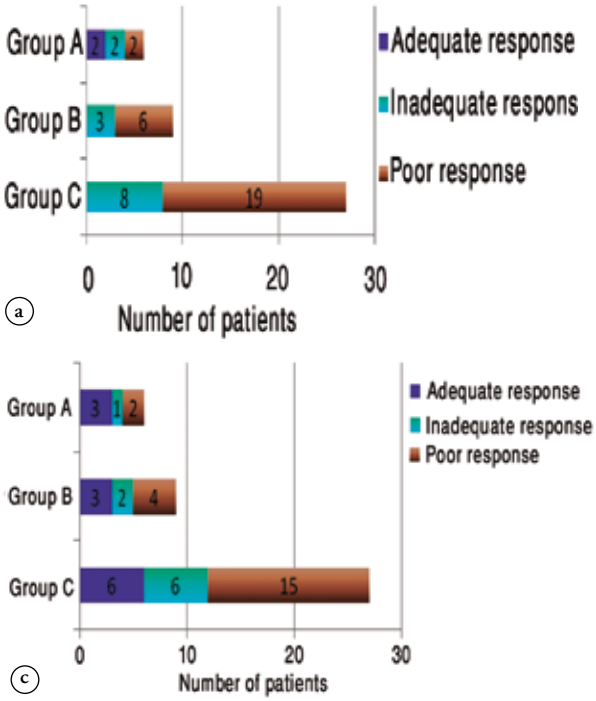
is still less than 75% of affected scalp, treatment was discontinued. If regrowth was 75% or more of affected scalp after 24 or 36 weeks of treatment, the intervals between pulses was increased gradually until they maintained their hair for 24 weeks without therapy. Responses were analyzed in relation to *AA* pattern, age of treatment, age of onset, gender, duration of disease, presence of previous episodes, status of alopecia (stable or progressive), personal history of atopy, personal history of autoimmune diseases, family history of alopecia areata, family history of autoimmune diseases, response to previous treatment, presence of nail involvement, presence of subclinical hypothyroidism, presence of thyroid auto antibodies, positive antinuclear antibodies, ferritin level, immunoglobulin E level and the presence and degree of dermal fibrosis, inflammation and epidermal follicular plugging.

All data were analyzed using the Statistical Package for Social Sciences version 16 (SPSS Inc., Chicago, IL, USA). Demographic variables were expressed as mean, standard deviation, and percentages. Fisher exact test and Chi-square test was performed to determine significance between variables. A $p<0.05$ was considered statistically significant.

Results. A total of 42 patients (20 females and 22 males) were included in this study. The overall mean age was 19.5 years. (**Table 1**). **Figure 1** summarizes the outcome at 12, 24, and 36 months of treatment with the 3 different regimens of pulse steroids. Four (9.5%) patients withdraw from the study. They were analyzed according to their last visit seen. At 36 weeks, 12 (28.6%) patients had adequate response, 9 (21.4%) had inadequate response, and 21 (50%) patients including the patients who withdraw had poor response. Among patients with *AU*, 10 (31%) showed adequate response (**Figures 2 & 3**), 7 (22%) inadequate, and 15 (47%) poor. Two out of 4 patients with *AT*, showed inadequate and 2 poor response (50% each). Among patients with *OA* 2 (33%) showed adequate, and 4 (67%) poor response. Although the percentage of adequate responders at 36 weeks were different among different therapeutic groups (3 [50%] in group A, 3 [33%] in group B, and 6 (22 %) in group C), the response rate comparing the adequate responders to inadequate and poor responders was not statistically significant between treatment groups ($p=0.371$). There were statistically significant differences in age of onset, duration of the disease and presence of subclinical hypothyroidism in between different response groups. Adequate responders were significantly older compared to inadequate and poor responders (16.81 ± 5.69 years versus 11.18 ± 7.07 years, $p=0.019$, 95% confidence interval [CI] of the difference=1.49-9.78). Adequate responders had significantly shorter

Table 1 - Demographics and study groups of patients included in a study of *Alopecia areata* at the Dermatology Department of King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia.

Characteristics	Group A (3 days/2 weeks) n=6	Group B (2 days/3 weeks) n=9	Group C (3 days/3 weeks) n=27	Total n=42
Age in years, mean ± SD	18.3 ± 5.9	20.9 ± 6.4	19.4 ± 8.1	**19.5 ± 7.4**
Age of onset in years, mean ±SD	13.5 ± 3.8	11.3 ± 6.1	11.9 ± 8.7	**12 ± 7.553**
Gender, female:male ratio	3:3	3:6	14:13	**20:22**
Duration of disease, mean ± SD	4.9 ± 3.7	9.7 ± 5.2	7.5 ± 4.5	**7.6 ± 4.7**
Previous episodes of *Alopecia areata*, n (%)	3 (50.0)	7 (77.8)	4 (14.8)	**14 (33.3)**
Personal history of atopy, n (%)	3 (50.0)	3 (33.3)	16 (59.3)	**22 (52.4)**
Autoimmune thyroiditis, n (%)	2 (33.3)	4 (44.4)	9 (33.3)	**15 (35.7)**
Subclinical hypothyroidism, n (%)	2 (33.3)	2 (22.2)	7 (25.9)	**11 (26.2)**
Nail involvement, n (%)	3 (50.0)	6 (66.7)	14 (51.9)	**23 (54.8)**
Family history of *Alopecia areata*, n (%)	0.0	3 (33.3)	8 (29.6)	**11 (26.2)**
Family history of autoimmune disease, n (%)	0.0	1 (11.1)	7 (25.9)	**8 (19.0)**
Alopecia areata pattern, n (%)				
Alopecia universalis	4 (66.7)	8 (88.9)	20 (74.1)	**32 (76.2)**
Alopecia totalis	0.0	0.0	4 (14.8)	**4 (9.5)**
Alopecia ophiasis	2 (33.3)	1 (11.1)	3 (11.1)	**6 (13.3)**



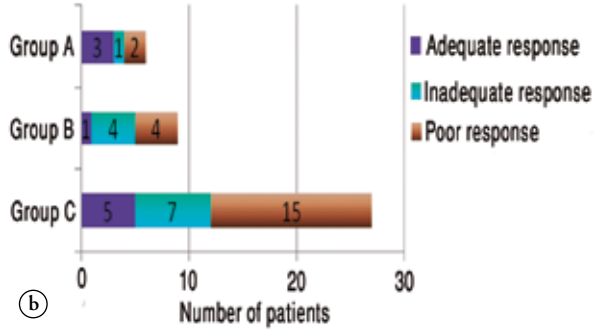


Figure 1 - Percentage of hair regrowth in the affected areas at **a**) 12, **b**) 24, and **c**) 36 weeks of treatment with different regimens of pulse steroid.

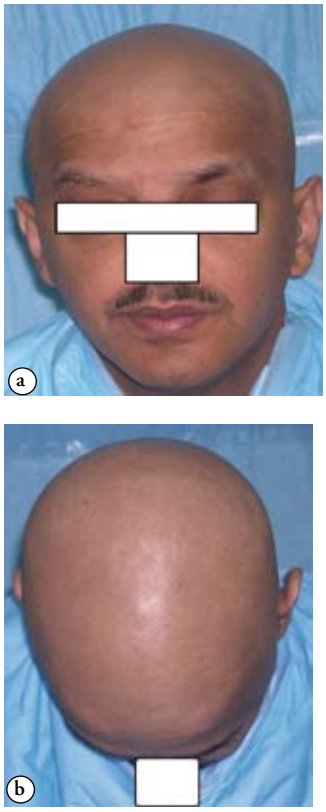


Figure 2 - *Alopecia totalis* (baseline): **a**) frontal view, **b**) crown view.

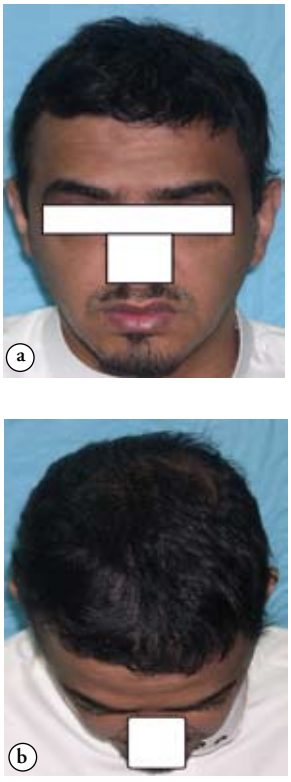


Figure 3 - Regrowth of hair at 36 weeks in a patient that underwent pulse steroid treatment : **a**) frontal view, **b**) crown view.

duration of the disease compared to inadequate and poor responders (5.3 ± 3.2 years versus 8.7 ± 4.6 years, p=0.023, 95% CI of the difference= -6.3 - -0.48).

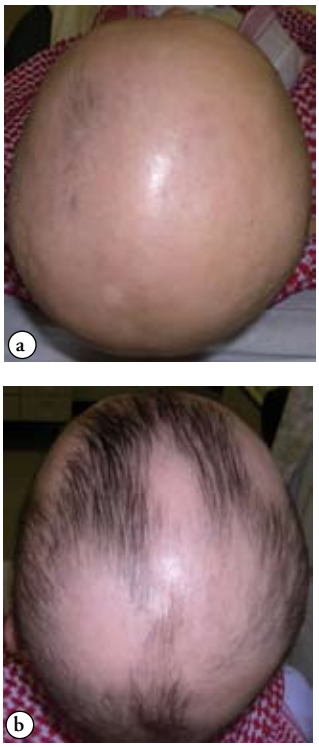


Figure 4 - Diffuse regrowth of terminal hair sparing multiple oval areas: **a**) baseline, and **b**) after treatment on patients that underwent pulse steroid treatment.

The presence of subclinical hypothyroidism (TSH >4 mIU/L) was statistically significant among inadequate and poor responders (p=0.011 by Fisher's exact test). Different pattern of hair regrowth were noted. Complete regrowth of terminal hair was observed in 5 (12%) patients, patchy regrowth of terminal hair in 11(26.2%) patients, and diffuse regrowth of fine hair in 2 (4.8%) patients. In addition, diffuse regrowth of terminal hair sparing multiple oval areas, some of which with a targetoid appearance, that continued to be resistant to therapy in spite of continuous treatment was seen in 8 (19%) patients (**Figure 4**). Diffuse regrowth of terminal hair sparing ophiasic areas was seen in 8 (19%) patients which included the occipital area (n=7) and parietal area (n=1); and no hair regrowth in 8 (19%) patients. Regrowth of white hair was seen in 2 patients (4.8%). Of note, only 2 patients had almost 100% regrowth. One of them maintained hair regrowth up to 2 years off-treatment, the other patient had mild relapse 6 months off-treatment. Among 34 patients who showed any degrees of hair regrowth, follow up was carried out for 1-4 years off-treatment to assess for maintenance of outcome. Of these, 13 (38.2%) patients relapsed, 5 (14.7%) patients developed moderate hair fall, 3 (8.8%) patients developed mild hair fall, 7 (20.1%) patients maintained their hair regrowth and 6 (17.6%) patients were lost to follow up (**Table 2**). The time to relapse whether on or off treatment varied from patient to patient, and was unpredictable. Some patients relapsed shortly after the induction phase while others kept their regrown hair for 4 years off-treatment. Relapse

Table 2 - Follow up and relapse rates with any hair regrowth, one to 4 years off-treatment of patients that received pulse steroid treatment at the Dermatology Department of King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia.

Characteristics	Group A	Group B (%)	Group C	Total
Hair regrowth	4	7	23	**34**
Adequate	3	3	6	**12**
Less than adequate	1	4	17	**22**
No hair regrowth	2	2	4	**8**
All lost to follow up (%)= adequate responder (%) + less than adequate responder (%)	0 = 0 + 0	1 (14.3) = 1 (14.3) + 0 (0)	5 (21.7) = 1 (4.3) + 4 (17.4)	**6 (17.6) = 2 + 4**
All maintained outcome (%) = adequate responder (%) + less than adequate responder (%)	2 (50)=2 (50) + 0 (0)	2 (28.6) = 0 (0) + 2 (28.6)	3 (13) = 1 (4.3) + 2 (8.7)	**7 (20.6) = 3 + 4**
All mild hair fall (%) = adequate responder (%) + less than adequate responder (%)	0 = 0 + 0	1 (14.3) = 0 (0) + 1 (14.3)	2 (8.7) = 2 (8.7) + 0 (0)	**3 (8.8) = 2 + 1**
All moderate hair fall (%)= adequate responder (%) + less than adequate responder(%)	1 (25) = 1 (25) + 0 (0)	2 (28.6) = 2 (28.6) + 0 (0)	2 (8.7) = 0 (0) + 2 (8.7)	**5 (14.7) = 3 + 2**
All relapsed (%)= adequate responder(%) + less than adequate responder(%)	1 (25) = 0 (0) + 1 (25)	1 (14.3) = 0 (0) + 1 (14.3)	11 (47.8) = 2 (8.7) + 9 (39.1)	**13 (38.2) = 2 + 11**

Table 3 - Summary of adverse events in 42 patients on oral mega pulse methyl prednisolone found in this study conducted at the Dermatology Department of King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia.

Adverse events	n (%)
Fatigue	27 (64.3)
Weight gain	19 (45.2)
Steroid induced acne	15 (35.7)
Sleep disturbances	14 (33.3)
Irritability, heart burn	9 (21.4) each
Dyspnea, bone ache	7 (16.7) each
Striae, headache, dizziness, lethargy arthralgia, mild cutaneous infection	6 (14.3) each
Nausea	5 (11.9)
Miscellaneous (anxiety, mood swinging, abnormal menses, palpitation, mild abdominal pain, epigastric pain, stomach upset, vomiting, increased or decreased appetite, metallic taste, hiccup, pruritus, flushing, hotness of the feet, muscle cramp, sweating, paresthesia, blurred vision, reduced concentration, pneumonia, diabetes mellitus, early cataract, hyperlipidemia)	Each ≤3 (≤7.1)

rate was not related to pattern of hair regrowth, and though it was relatively lower in group A and B than in group C, however, this was not statistically significant (p=0.494). Pulse steroid treatment was relatively tolerated in treatment groups B and C. Overall, 40 (95%) patients reported 186 adverse events (**Table 3**). The most common side effect was fatigue (n=27, 64%) starting on the last day of each pulse treatment, and lasted 3 days after each pulse. It decreased in severity with subsequent therapeutic pulses. It was followed by weight gain (n=19, 45%), steroid induced acne (n=15, 35.7%), and sleep disturbances (n=14, 33%). Irritability, lethargy, dizziness, headache, anxiety, mood swinging, shortness of breath, palpitation, mild abdominal pain, stomach upset, heart burn, nausea, vomiting, increased or reduced appetite, metallic taste, hiccup, pruritus, flushing, hotness in feet, muscle cramp, bony pain, arthralgia, sweating, paresthesia, blurred vision, and reduced concentration were less frequently reported. They lasted 3 days after each pulse, then spontaneously disappeared. Other side effects included striae (n=6, 14%), mild cutaneous infection (n=6, 14%), abnormal menses (n=2, 4.8%), pneumonia (n=1, 2.4%), early cataract (n=1, 2.4%), hyperlipidemia (n=1, 2.4%) and diabetes mellitus (n=1, 2.4%). Significant differences in incidence of adverse events were observed between treatment groups A and C. Incidence of reduced concentration (p=0.0018), stomach upset (p=0.0018), increased appetite (p=0.0018), metallic taste (p= 0.0018), and arthralgia (p=0.010) were more common in treatment group A. One patient discontinued therapy due to pneumonia, and the other 3 discontinued because of the frequent hospital visits, which affected school and work performances.

Discussion. High dose pulse GC is an alternative method of GC delivery that proved to be well-tolerated with a rapid and potent therapeutic efficacy in several diseases. The regimens for pulse GC administration and the GC used vary widely with little uniformity among the published studies and reports.[8] The MP, prednisolone and dexamethasone are the 3 GCs most frequently used in pulse regimens.[8-10] The MP is approximately 25% more potent than prednisolone in terms of anti-inflammatory effects of these GCs.[10] A recent study has shown that in vitro suppressive potency of MP on the blastogenesis of peripheral-blood lymphocyte from renal transplant recipient is more than 10 folds superior to prednisolone.[9,10] Lower mineralocorticoid activity of MP, when compared to prednisolone and dexamethasone is an additional benefit of MP.[9]

Several randomized trials compared high dose oral versus intravenous GC and showed no difference in clinical response.[8] The relative bioavailability of the orally administered MP sodium succinate was 69.2% of that of the intravenous form.[7] It is not clear whether the pharmacokinetics of intravenous MP is superior enough to justify the inconvenience of IV administration. Most previous studies preferred the intravenous route to the oral route of pulse GCs due to the uncertainty of its bioavailability, and the gastric effect of the latter. However, recently it has been proven that short term high oral prednisolone is not associated with greater gastric damage as measured with permeability test, than intravenous MP.[11] In addition, oral administration decreases the cost and inconvenience of steroid therapy, and the cost and complexity of the clinical trial needed to study other aspects of GC pulse therapy. Prospective studies in which pulse GC was used in *AA* involved

small numbers of patients, and were inconsistent with regard to type, dosage, frequency, or duration of therapy. Most studies used single pulse /cycle, or few pluses given monthly or at irregular intervals with no or only short follow up. The dosage of GC varied widely, but lower doses were given more commonly regardless of the weight of the patients.[12-15] The lack of consistency of these studies made it difficult to conclude with certainty on the efficacy of such a valuable and relatively safe therapeutic modality in the treatment of such sinister subsets of *AA*. Contrary to a previous study carried out by Al-Khawajah[16] on AA association, 52.4% of our patients had atopic diathesis compared to 13% by Al-Khawajah, and 35.7% had autoimmune thyroiditis (5.4% in Al-Khawajah).[16] Al-Khawajah study was carried out on any *AA* regardless of the subtype, while this current study was carried out on severe forms, this explains the different figures noted. Goh et al[17] found that atopic dermatitis (p=0.021), and thyroid disease (p=0.012) were significantly associated with *AT* or *AU*. Barahmani et al[18] also found that a history of atopic dermatitis, or a history of hypothyroidism was statistically significant associated with *AT* or *AU*. They also found that the risk of having any subtype of *AA* was almost double among those with a history of atopic dermatitis, and the risk was almost 3 times greater for *AT* or *AU*.[18]

Our study showed that mega pulses MP given as 15 mg/kg IBW/day orally for 2-3 days every 2-3 weeks led to adequate hair regrowth in 28.6% of patients within 6-9 months of treatment. Our result is comparable with that of topical diphenylcyclopropenone in a prospective open clinical trial by Sotiriadis[19]. There was no significant difference in response between *AU*, *AT* and *OA*. Therapy was more effective in patients with later onset (16.81± 5.69 years versus 11.18 ± 7.07 years), short duration (5.3 ± 3.2 years versus 8.7 ± 4.6 years, and normal thyroid function. Most previous studies reported a cosmetically worthwhile response of extensive patchy *AA* to pulse GC therapy in approximately 60% of patients, but less than 10% of the patients with *AU*, *AT,* and *OA* responded.[2,12,13,20] Longer duration of *AA* (more than 2 years), younger age at onset, extensive hair loss, ophiasis, nail involvement, atopy, presence of other immune diseases, and family history of *AA* are known to be associated with poor therapeutic response.[3,21,22] A high relapse rate is expected after discontinuation of treatment. We found a relapse in 38% of the responders at one year follow up, which is high compared with relapses reported previously by Nakajima et al (21.4%) and others.[23,24] This could be related to their short follow up. On the other hand, the relapse rate was less than that reported by Kurasawa et al, and others that is reaching up to 100% in *AT* and *AU*.[15,25,26] Consistent with previous reports, we noted that pulsed systemic GC therapy modifies the initial course of severe *AA* but does not generally influence the long term outcome. This suggests that severe AA management necessitates a long term maintenance treatment similar to other chronic autoimmune disorders.[26,27]

We noted different pattern of hair regrowth including targetoid and concentric patterns which has been previously reported.[27,28] Another pattern that was not previously described is diffuse regrowth of terminal hair sparing multiple oval areas in-between that continued to be resistant to therapy in spite of continuous treatment. This could be due to irreversible damage to hair follicles secondary to long standing, severe inflammation at the affected sites. Side effects were seen in 95% of patients treated with oral mega pulse MP, which is higher, albeit less severe, than the figures reported from other studies.[29] Although none of our patients had serious adverse events from pulse GC therapy, this treatment may cause significant adverse reactions. In contrast to previous reports, we found significant increase in body weight, fatigue, acne, and sleep disturbance.[29] There were no significant abnormalities detected in ECG, chest, or sinuses x-ray, DEXA scan and synacthen test. Only one case of early cataract was detected by ophthalmologic examination, one patient developed pneumonia, one patient had hyperlipidemia, and one patient had blood sugar values consistent with diabetes mellitus. Keeping in consideration that the randomization method was not optimal in this study and the number of patients is low, the results may have some biases. We suggest conducting further controlled studies on a larger scale of patients to confirm the reliability of such regimen in the management of severe forms of *AA*.

In conclusion, our study shows that in severe cases of *AA*, screening for atopy and autoimmune thyroiditis should be considered. Oral mega pulse MP is a relatively tolerated therapeutic option for severe forms of *AA*, but not using group A regimen with the most frequent pulse cycles (that is, 3 consecutive days once every 2 weeks). However, many patients will relapse regardless of maintenance therapy. The main question regarding treatment of severe *AA* remains a big challenge that is, how to maintain hair growth after successful induction.

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