



Manuscript ID:ZUMJ-2410-3614

DOI: 10.21608/ZUMJ.2024.325505.3614

**ORIGINAL ARTICLE**

## Treatment of Alopecia Areata using Transdermal Delivery of 5-Fluorouracil by Fractional CO<sub>2</sub> Laser versus Intralesional Injection of 5-Fluorouracil

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**Submit date: 02-10-2024**

**Revise date: 24-10-2024**

**Accept date: 27-10-2024**

### ABSTRACT

**Background:** An intricate autoimmune disease called alopecia areata causes hair loss. Even though there are numerous therapeutic alternatives, the most of them have significant side effects and/or poor efficacy. This promotes the continuous development of novel therapies. The purpose of this study was to compare intralesional injection of 5-fluorouracil with transdermal delivery of the drug using fractional CO<sub>2</sub> laser for the treatment of alopecia areata. **Methods:** The study was clinical trial. It included 52 AA patients were divided into two groups each group 26 patients Group I (Transdermal of 5-fluorouracil following fractional laser) and Group II (Cases injected with intralesional 5-Fluorouracil). Clinical examination was done with assessment of disease severity at baseline and each visit using Severity of Alopecia Tool Score (SALT). Digital photographs of the lesions were performed at baseline and at weeks 2,4,6,8 &12 for results evaluation. **Results:** Regarding response to treatment : There was a statistical significant difference among both groups regarding to response to treatment, as 15.4% of group II showed no response versus 7.7% of group I, while 61.5% of group I showed excellent response versus 23.1% of group II. And there was a statistical significance decrease in SALT score in both groups post treatment compared to pre by (65.5% & 34.1% respectively). **Conclusions:** Treatment of Alopecia Areata using transdermal delivery of 5-Fluorouracil by fractional CO<sub>2</sub> laser showed excellent response compared by intralesional injection of 5-Fluorouracil.

**Keywords:** Alopecia areata , Fractional laser , 5-Fluorouracil

### INTRODUCTION

Alopecia areata (AA) is a common cause of non-scarring alopecia that affects mainly the scalp, but other hairy areas may be also involved [1]. Although affliction of all scalp hairs (alopecia totalis [AT]) or all scalp and body hairs (alopecia universalis [AU]) may occur, it typically manifests as a patchwork pattern [2].

Though its precise cause is unknown, it is generally agreed that AA is an organ-specific autoimmune disease that affects those who are genetically susceptible to it. Environmental triggers include emotional stress, anemia, parasitic infestations, and thyroid issues [3].

About 2% of the general population has alopecia areata (AA), with no discernible sex, racial, or age group predispositions. In an investigation of Thompson et al. [4], Compared to adults, the pediatric age group had a decreased prevalence of AA. This result might lend credence to the theory

that AA is becoming more and more common over time. Recent research on the increased ratio of AA may provide evidence that the frequency of AA and its subtypes differs geographically [2].

The prognosis for AA sufferers varies; some may have spontaneous regrowth after a certain amount of time, while others may have a poor prognosis and a worsening condition. Childhood onset, severe disease, ophiasis pattern, and aberrant nail growth are all considered poor prognostic markers [5].

In the past, fractional laser treatment for hair loss has gained a lot of popularity. Because some wavelengths of laser light have been shown to stimulate hair growth, the procedure has also been touted as a prophylactic step against AA [6].

If fractional lasers are used under the right conditions, they can promote hair growth. While the exact mechanisms by which certain fractional lasers affect hair regeneration remain poorly

understood, trauma-stimulated wound healing is most likely the cause. The progeny of hair follicle stem cells migrate to the epidermal defect and encourage re-epithelialization. Anagen phase accelerates the healing of cutaneous wounds and promotes the formation of additional hair follicles following tissue damage [7]. Analogous to uracil, a naturally occurring pyrimidine, 5-fluorouracil (5-FU) is an antimetabolite that is metabolized through the same mechanisms as uracil [8].

#### **Aim of the work:**

This study aimed to compare intralesional injection of 5-fluorouracil with transdermal delivery of the drug using fractional CO<sub>2</sub> laser for the treatment of alopecia areata.

#### **Methods**

This self matched clinical trial study was conducted at Dermatology, Venereology and Andrology Department Faculty of medicine, Zagazig University during the period of from May 2023 to June 2024 of the fifty two patients, complaining of AA of the scalp or the beard, with two or more patches collected from Dermatology Outpatient Clinic, only Forty Eight completed six sessions of the treatment. The remaining four patients did not turn up. These patients were contacted and they did not wish to continue with the treatment method because they have pain and pruritis between sessions. Up to our knowledge this study was the first to compare treatment of Alopecia Areata using transdermal delivery of 5-Fluorouracil by fractional CO<sub>2</sub> laser versus intralesional injection of 5-Fluorouracil. An informed written consent was signed by all participants and the study design was approved by the ethical committee, Faculty of medicine, Zagazig University (IRB#10595-26-3-2023). The work was finished in compliance with the World Medical Association's code of ethics for research involving human subjects, the Declaration of Helsinki.

The inclusion criteria include patients diagnosed with Alopecia areata (AA) of the scalp or the beard who were between the ages of > 18 years old of both sexes. While, the exclusion criteria include, age less than 18 years old, Active infectious diseases in the treated locations, pregnancy and lactation, and other forms of alopecia [such as totalis, universalis, ophiasis, and androgenetic alopecia].

**Sample Size** :According to mean SD of SALT severity score and assuming the frequency of improvement was 46.7% vs 86.7% in laser vs intralesional injection. At 80% power and 95% cl, the estimated sample will be 52 cases, 26 cases in each group. Open epi

**Group I:** includes 26 patients were treated with fractional CO<sub>2</sub> laser followed by topical application of 5-fluorouracil. **Group II:** includes 26 patients were treated with intralesional injection of 5-Fluorouracil.

All patients were subjected to history taking, and to local clinical and dermoscopic examination of the lesion(s), Dermoscopic Dermlite DL4 was used to assess disease activity before and after treatment.

#### **Follow up assessment:**

A professional photographic assessment was conducted using a high-quality camera at the beginning of treatment and during every session. The Severity of Alopecia SALT score was used to assess the clinical severity of AA. It was computed by visually calculating the percentage of scalp hair loss in each of the four quadrants of the scalp, adding the values together, and calculating a maximum score of 100%. SALT categories described: on hair loss =0%; limited=1-20%; moderate = 21-49%; severe=50-94% and very severe = 95-100%. the following percentages of scalp hair regrowth are possible: A0 = no change or further loss, A1 = 1%–24% regrowth, A2 = 25%–49% regrowth, A3 = 50%–74% regrowth, A4 = 75%–99% regrowth, and A5 = 100% regrowth as shown in **figure 1**.

For dermoscopic imaging, a handheld dermatoscope with polarized light was utilized. A digital camera was used to take the photos. At the beginning of each month's treatment and at its conclusion, the pictures were taken. After digital photos were saved to a computer, they were checked to see if there were any black spots, broken hairs, exclamation marks or examined for signs of longstanding disease as yellow dots and the presence of new hair growth signs as upright regrowing hairs, pigtail hairs and vellus hairs .

#### **Technique:**

The patients in group I were applied fractional CO<sub>2</sub> Dermal Optical Thermolysis (DOT) fractional scanning mode, one pulse, power 30w, dwell period 300 μs, smart stack 1, emission mode Deka pulse (DP), and spacing 500 μm were the laser characteristics that were employed.

Patches were treated with ablative fractional CO<sub>2</sub> laser followed by topical 5-fluorouracil 50-mg/mL solution in group I, Patches were treated with intralesional injection of 5-Fluorouracil 50-mg/mL solution by concentration 0.1ml/cm<sup>2</sup> in group II .

Up to six treatment sessions were possible, or until full hair regrowth was attained, by repeating the procedures every two weeks. Following the completion of all six sessions, a clinical evaluation and digital and dermoscopic photos

were taken at baseline. In the interim between sessions, the patients received no topical treatments.

The following percentages of scalp hair regeneration can be used to evaluate hair restoration at each follow-up visit: A1 = 1%–24% regrowth, A0 = no change or further loss, A2 = 25%–49% regrowth, A3 = 50%–74% regrowth, A4 = 75%–99% regrowth, and A5 = 100% regrowth according to difference in SALT score between first and last sessions.

**Also, MacDonald Hull and Norris (1988)** grading system was done as follows:

**Grade 0:** no hair regrowth (no response),

**Grade 1:** regrowth of vellus hair (Mild response),

**Grade 2:** regeneration of terminal hair with scant pigmentation (Moderate response),

**Grade 3:** terminal hair regrowth in clusters (Good response),

**Grade 4:** total terminal hair growth over the alopecia patch (Excellent response).

#### **Pre/Post-operative Care:**

The patients were told to wash their heads and not to put anything on them before the session. Following the session, the patients were told not to wear headgear or direct sunlight, and to apply a topical antibiotic (fungicidal acid).

#### **Statistical Analysis:**

Data were checked, entered and analyzed using SPSS version 23 for data processing. Data were expressed as number and percentage for qualitative variables and mean + standard deviation (SD) for quantitative one. Mann Whitney test was used to calculate difference between quantitative variables in not normally distributed data in two groups; Chi-square test ( $\chi^2$ ), Z-test for percentage to compare percentage of outcome between the two groups. The significance level was established at a threshold of  $P < 0.05$ .

## **RESULTS**

In terms of age or sex distribution, there were no statistically significant variations between the groups under study (Table 1). Between the groups under study, there were no statistically significant differences in terms of disease duration, number of patches, or lesion site (Table 1).

Table 2; showed that there was no statistical significance differences in percent of hair growth. While frequency of A5 cases were higher among cases of group I (transdermal 5-fluorouracil following fractional laser) than cases injected with 5-fluorouracil alone (61.5% & 23.1% respectively).

Table 3; demonstrated that there were no statistically significant differences in SALT scores, either before or after therapy, between the groups under study. However, the SALT scores in both groups decreased statistically significantly after therapy as opposed to before by (65.5% & 34.1% respectively).

Table 4; demonstrated that, both before and after therapy, there were no statistically significant changes between the groups under study on any of the items. When comparing the pre- and post-treatment differences in each group, it was found that the post-treatment black dot decreases in both groups were statistically significant by 55% and 45%, respectively. Also, there was a statistical significance decrease in broken hair in both groups post treatment compared to pre by 65% (group II) & 75% (group I). There was a statistical significance increase in Vellous hair in Group I post treatment compared to pre by 32%.

Table 5; showed that there was a statistical significant difference among both groups regarding to response to treatment, as 15.4% of group II showed no response versus 7.7% of group I, while 61.5% of group I showed excellent response versus 23.1% of group II.

#### **Case Presentation:**

**Case 1:** Male (20 years old) with single patch of Alopecia Areata over the back of the scalp. (A) Before treatment by fractional CO<sub>2</sub> laser followed by topical 5-FU. (B) After treatment (excellent response). (C) Dermoscopy before . (D) Dermoscopy after.

**Case 2:** Male ( 27 years old) with single patch of Alopecia Areata over the left side of the scalp. (A) Before treatment by fractional CO<sub>2</sub> laser followed by topical 5-FU. (B) After treatment (excellent response). (C) Dermoscopy before . (D) Dermoscopy after.

**Case 3:** Male (30 years old) with single patch of Alopecia Areata over the right side of the scalp. (A) Before treatment by intralesional injection of 5-FU (B) After treatment (moderate response). (C) Dermoscopy before . (D) Dermoscopy after.

**Case 4:** Male (38 years old) with single patch of Alopecia Areata over the beard. (A) Before treatment by intralesional injection of 5-FU. (B) After treatment (moderate response). (C) Dermoscopy before . (D) Dermoscopy after.

**Case 5:** Male (22 years old) with more patches of Alopecia Areata over the back the scalp. (A) Before treatment by intralesional injection of 5-FU (B) After treatment (no response). (C) Dermoscopy before . (D) Dermoscopy after.

**Table 1:** Demographic data of the studied groups:

Variable		Group I (n=26)		Group II (n=26)		KW	P
Age: (years)	Mean ± SD	29.5 ± 8.39		29.9 ± 7.71		0.049	0.947 NS
	Range	16 – 55		10 - 37			
Variable		No	%	No	%	χ <sup>2</sup>	P
Sex:	Female	3	11.5	2	7.7	0.211	0.635 NS
	Male	23	88.5	24	92.3		
<b>Clinical</b>							
Disease duration:	<1 month	10	38.5	7	26.9	2.01	0.362 NS
	1-6 month	15	57.7	19	73.1		
	>6month	1	3.8	0	0		
Number of patches:	1	24	92.3	24	92.3	1.36	0.517 NS
	2	1	3.8	2	7.7		
	3	1	3.8	0	0		
Site:	Beard	4	15.4	4	15.4	0.00	1.0 NS
	Scalp	22	84.6	22	84.6		

SD: Stander deviation,  
χ<sup>2</sup>: Chai square test.

Independent sample t-test,  
NS: Non significant (P>0.05)

**Table 2:** Percent of hair growth among the studied groups:

Variable		Group I (n=26)		Group II (n=26)		χ <sup>2</sup>	P
		No	%				
Percent of growth:	A0	2	7.7	4	15.4	8.22	0.09 NS
	A1	4	15.4	6	23.1		
	A3	1	3.8	2	7.7		
	A4	3	11.5	8	30.8		
	A5	16	61.5	6	23.1		

χ<sup>2</sup>: Chai square test.

NS: Non significant (P>0.05)

**Table 3:** SALT score pre & post treatment among the studied groups:

Variable		Group I (n=26)		Group II (n=26)		MW	P
SALT before:	Mean ± SD	4.02 ± 2.41		4.85 ± 3.24		0.651	0.533 NS
	Median	3.5		5			
	Range	2 - 6		2 – 7			
SALT after:	Mean ± SD	1.58 ± 1.84		1.45 ± 2.47		1.62	0.09 NS
	Median	3		0			
	Range	1 - 5		0 - 5			
<b>W</b>		<b>3.40</b>		<b>3.13</b>			
<b>P</b>		<b>0.001*</b>		<b>0.002*</b>			
<b>% of change</b>		<b>-65.5%</b>		<b>-34.1%</b>			

SD: Stander deviation,  
W: Paired Wilcoxon test  
\*: Significant (P<0.05)

MW: Mann Whitney test,  
NS: Non significant (P>0.05)

**Table 4:** Some dermoscopic findings results among the studied groups pre & post treatment:

Variable		Group I (n=26)		Group II (n=26)		$\chi^2$	P
		No	%	No	%		
<b>Black dots before:</b>	No	8	30.8	12	46.2	1.38	0.11 NS
	Yes	18	69.2	14	53.8		
<b>Black dots after:</b>	No	23	88.5	24	92.3	0.544	0.212
	Yes	3	11.5	2	7.7		
<b>P<sup>^</sup></b>		<b>&lt;0.001**</b>		<b>&lt;0.001</b>			
<b>% of change</b>		<b>-55%</b>		<b>-45%</b>			
<b>Broken hair before:</b>	No	2	7.7	6	23.1	1.17	0.21 NS
	Yes	24	92.3	20	76.9		
<b>Broken hair after:</b>	No	20	76.9	24	92.3	2.16	0.310 NS
	Yes	6	23.1	2	7.7		
<b>P<sup>^</sup></b>		<b>0.02*</b>		<b>0.006 S</b>			
<b>% of change</b>		<b>-70%</b>		<b>-65%</b>			
<b>Yellow dots before:</b>	No	21	80.8	22	84.6	0.68	0.71 NS
	Yes	5	19.2	4	15.4		
<b>Yellow dots after:</b>	No	21	80.8	26	100	0.444	0.211 NS
	Yes	5	19.2	0	0		
<b>P<sup>^</sup></b>		0.201		<b>0.211</b>	<b>NS</b>		
<b>% of change</b>		0%		<b>-10%</b>			
<b>Vellus hair before:</b>	No	18	69.2	22	84.6	3.12	0.21 NS
	Yes	8	30.8	4	15.4		
<b>Vellus hair After:</b>	No	24	92.3	22	84.6	0.416	0.321
	Yes	2	7.7	4	15.4		
<b>P<sup>^</sup></b>		<b>0.01*</b>		<b>0.13</b>	<b>NS</b>		
<b>% of change</b>		<b>32%</b>		<b>0%</b>			

$\chi^2$ : Chai square test.

NS: Non significant (P>0.05)

\*\* : highly significant (P<0.001)

P2: Group I versus Group III

P<sup>^</sup>:McNemar test

\*: Significant (P<0.05)

P1: Group I versus Group II

P3: Group II versus Group III

**Table 5:** Response to treatment among the studied groups:

		Group I (n=26)		Group II (n=26)		$\chi^2$	P
		No	%	No	%		
<b>Response:</b>	<b>No</b>	2	7.7	4	15.4	9.32	0.03 S
	<b>Mild</b>	4	15.4	6	23.1		
	<b>Moderate</b>	3	11.5	4	15.4		
	<b>Good</b>	1	3.8	6	23.1		
	<b>Excellent</b>	16	61.5	6	23.1		

$\chi^2$ : Chai square test. S: significant (P<0.05)



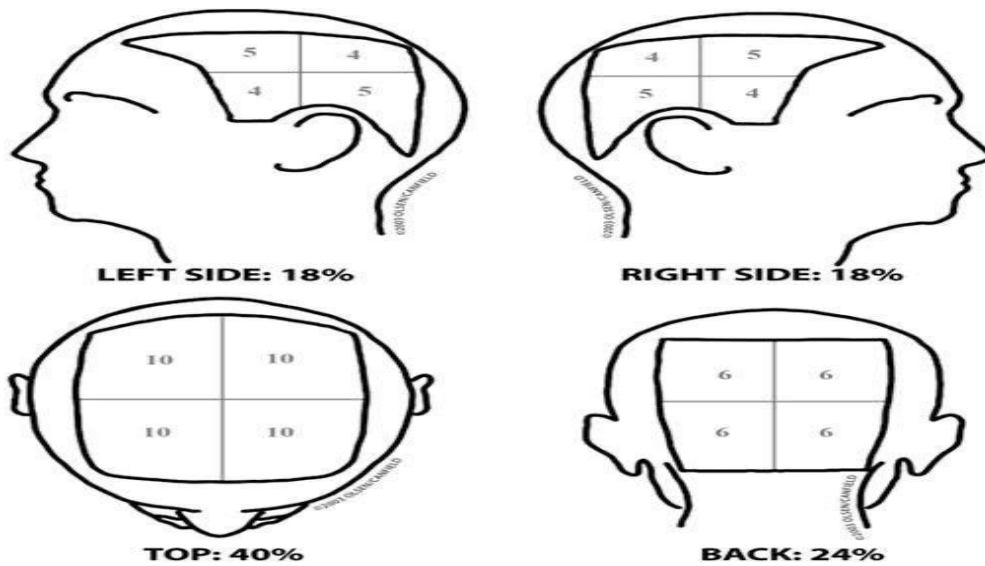
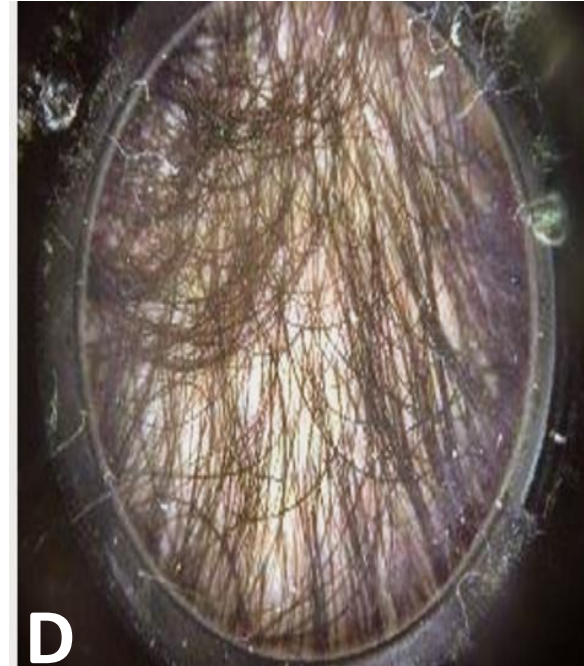


Figure 1: SALT score.

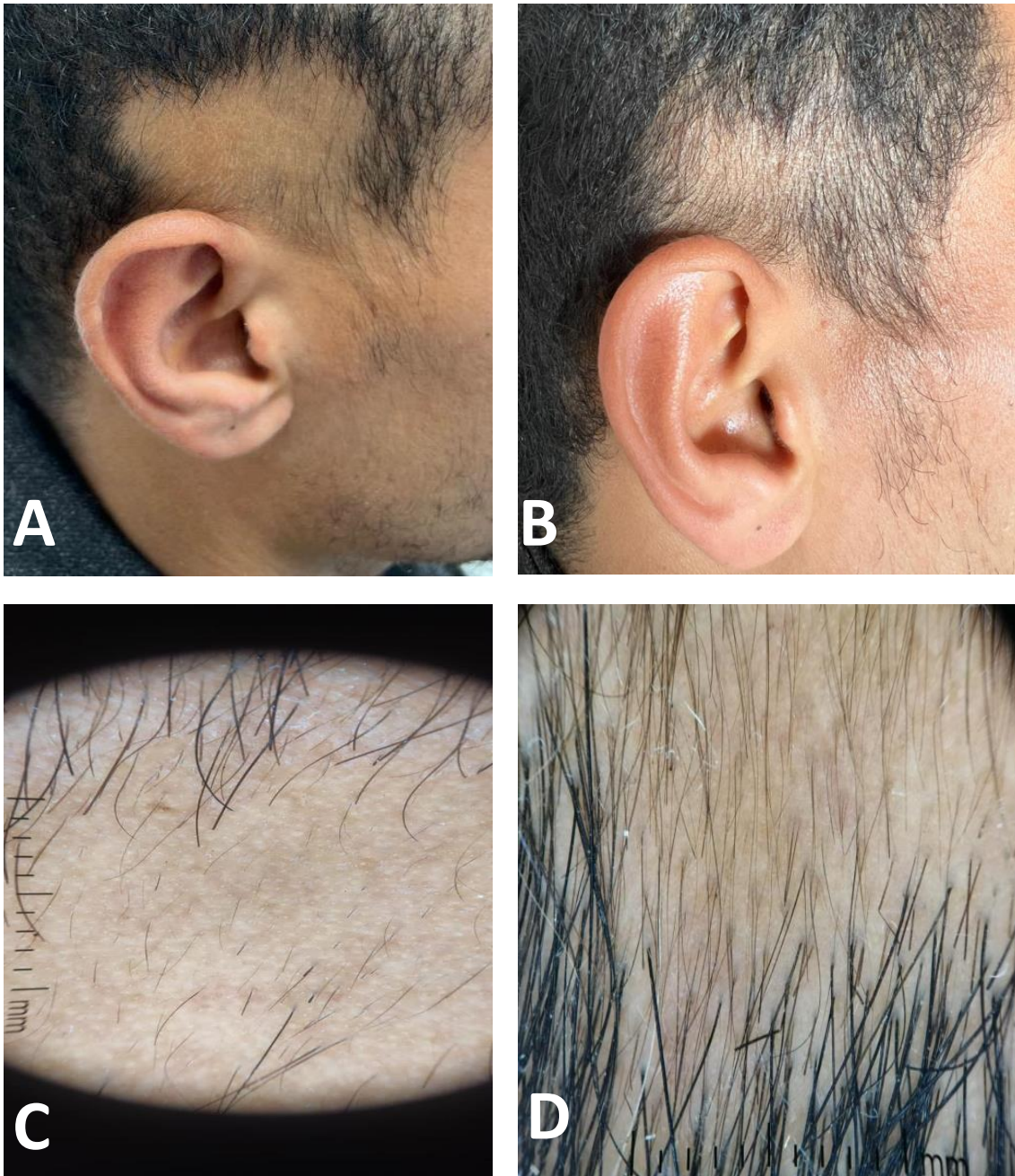


Case 1: **A**; Before treatment by fractional CO<sub>2</sub> laser followed by topical 5-FU. **B**; After treatment (excellent response). **C**; Dermoscopy before. **D**; Dermoscopy after.



**Case 2; A ;** Before treatment by fractional CO2 laser followed by topical 5-FU. **B;** After treatment (excellent response). **C;** Dermoscopy before. **D;** Dermoscopy after



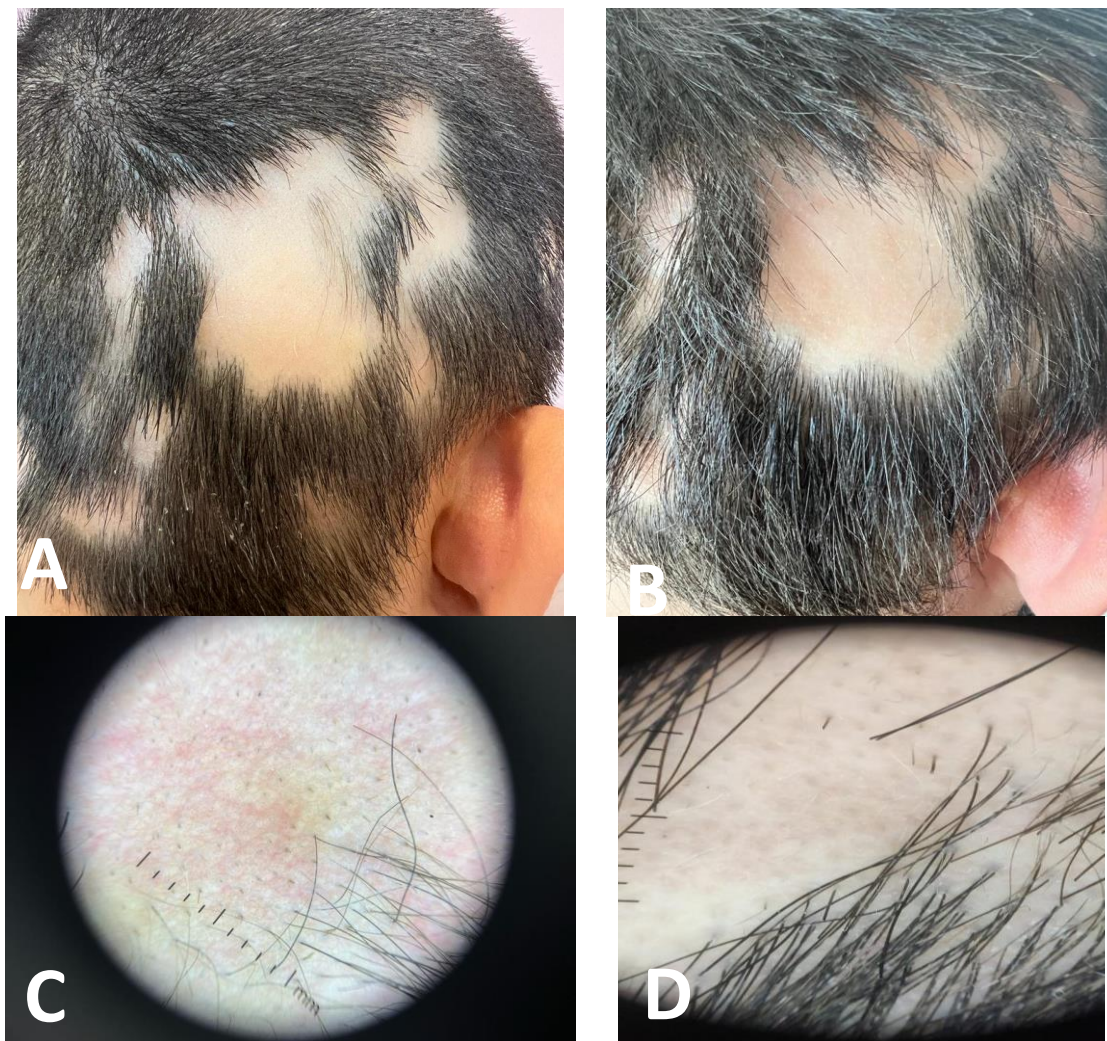


**Case 3; A;** Before treatment by intralesional injection of 5-FU. **B;** After treatment (moderate response). **C;** Dermoscopy before. **D;** Dermoscopy after.





**Case 4; A; Before treatment by intralesional injection of 5-FU. B ; After treatment (moderate response). C; Dermoscopy before . D; Dermoscopy after**



**Case 5; A ;** Before treatment by intralesional injection of 5-FU. **B ;** After treatment (no response). **C;** Dermoscopy before. **D;** Dermoscopy after.

### DISCUSSION

A unique, non-traditional treatment for AA is fractional laser[9]. That may cause T cell apoptosis, which would cause hair to grow back in AA [10-11].

In 1957, 5-fluorouracil, an analogue of fluorinated pyrimidine, was introduced as a novel kind of antimetabolite medication. 5-FU is recommended as an intralesional and topical treatment for a number of dermatological conditions [12].

Two groups of patients were formed. Team I (Transdermal of 5-fluorouracil following fractional laser) and Group II (Cases injected with intralesional 5-Fluorouracil).

Demographics data and personal characteristics of studied groups denoted that The age and sex distributions of the investigated groups did not differ statistically significantly. This was in accordance with *Meguid et al.* [13] Our investigation revealed that there was no discernible variation in the patients' demographic information.

This was in disagreement with the findings of El-Morsy et al. [14] whose study on AA patients included (60.0%) males and (40.0%) The majority of patients were under 30 years old, and the patients' ages ranged from 9.0 to 46.0 years among females. The study conducted by *Al-Mutairi and Eldin* [15]. The majority of AA patients were between the ages of 21 and 40, with 65.02% of the patients being men and 34.97% being women [16].

Reported also increased incidence of AA in men(68%) compared to women (32%) and majority of the patients were in the third decade of life.

On the other hand, a study by *Manolache and Benea* [17] reported a female predominance as they found that in the AA adult group, There were 18 male individuals (40%) and 27 female subjects (60%) total.

Our findings revealed that Clinical data of the disease among studied groups, Between the groups under study, there were no statistically significant differences in terms of disease



duration, number of patches, or lesion site. They also found that there are no significant differences were also found in the age of onset, mean disease duration, or type of AA by sex or ethnicity [18].

The SALT scores of the investigated groups did not differ statistically significantly before or after therapy. However, the SALT scores of both groups were statistically significantly lower after therapy than they were before (65.5% & 34.1%, respectively). comparable to the outcomes of *Hamdino et al.* [19], who found that There was a statistically insignificant difference between both groups regarding SALT score before treatment, at end of sessions (12 weeks), and at 3-months follow up.

There was no statistical significance differences in percent of hair growth. While frequency of A5 cases were higher among cases of group I (transdermal 5-fluorouracil following fractional laser) than cases injected with 5-fluorouracil alone (61.5% & 23.1% respectively).

These results agreed with *Meguid et al.* [13] who gave such description, The mean grade of the lesions in all groups increased significantly after treatment compared to the baseline, according to MacDonald Hull and Norris grading, which was in agreement with *El-Husseiny et al.* [20], They reported that the patches treated with FCL significantly improved; 60% of their patients showed improvements greater than 75%.

Nouh et al. found that 40 AA patients receiving FCL alone had a significantly higher re-growth scale; 15% of these patients showed excellent response ( $\geq 75\%$ ) [21].

In our study only 3 cases had previous treatment with minoxidil in group I and group II only 4 cases had previous treatment with local corticosteroid.

Trichoscopy is a noninvasive diagnostic tool that may distinguish between progressive and stationary diseases and predict the onset of disease recovery before any clinical symptoms appear [22].

Dermoscopic findings of examined groups. Before and after therapy, there were no statistically significant differences found in any of the items analyzed between the groups under study. When comparing the pre- and post-treatment differences in each group, it was found that the post-treatment black dot decreases in both groups were statistically significant by 55% and 45%, respectively. Also, there was a statistical significance decrease in broken hair in both groups post treatment compared to pre by 65% (group II) & 75% (group I). There was a statistical significance increase in Vellous hair in Group I post treatment compared to pre by 32%. similar to

result of *Abd-ElRaheem et al.* [23]; *Rashad et al.* [24] who observed that the most common dermoscopic traits in AA were short vellus hairs, YD, BD, BH, and EMH. Significant post-treatment declines in YD, BD, BH, and EMH were observed in all groups, and in 79.6% of patients, terminal hairs had significantly appeared relative to baseline. These findings concurred with other studies' findings [19,23].

Regarding the two groups' responses to therapy, there was a statistically significant difference in our investigation, as 15.4% of group II showed no response versus 7.7% of group I, while 61.5% of group I showed excellent response versus 23.1% of group II.

In agreement with *Meguid et al.* [13] Their post-treatment AASI was significantly lower than baseline after receiving FCL + TA therapy. The average improvement percentage was  $72.6 \pm 36.5$ . A remarkable improvement of  $\geq 75\%$  was attained by 62.5%.

On the contrary, *Yalici-Armagan and Elcin* [25] stated that AA could not be successfully treated by FCL. Their lower results might be explained by the fact that they only included patients whose diseases had been ongoing for more than a year.

Soror et al. found a noteworthy improvement in grading AA patches treated by FCL plus TA, which is consistent with our findings [26].

Also, *Abd ElKawy et al.* [27] detected  $> 75\%$  improvement in 56.7% of AA patches treated with FCL + TA (based on the severity of the alopecia assessment).

In our study we found minimal or no side effects similar results were observed in the study of *Abd El-Hamed* [28].

In contrast to our findings, they said that 4.6% of cases had atrophy and 7.5% of cases had telangiectasia. Furthermore, the investigation of *Kuldeep et al.* [29] noted atrophy at the locations where TrA is injected. Furthermore, *Ganjoo et al.* [30] Dermoscopy revealed telangiectasia in 3% of cases and atrophy in 16%.

To the best of our knowledge, our research demonstrates the use of fractional CO<sub>2</sub> laser transdermal delivery of 5-fluorouracil for the treatment of alopecia areata showed excellent response compared by intralesional injection of 5-Fluorouracil.

There were some limitations in this study. This clinical trial study was conducted at a single centre with a small period for follow-up, so we recommended future larger large number of studies must be done to analyze the clinical outcomes of these treatment methods to aid in the improvement of the recent protocols of management of alopecia areata. To follow up the



patients for longer periods to assess the improvement and recurrence of lesions after stoppage of treatment.

### CONCLUSION

Our conclusion is treatment of Alopecia Areata using transdermal When 5-fluorouracil was delivered via fractional CO<sub>2</sub> laser, it performed better than when it was injected intralesionally.

### CONFLICT OF INTEREST

The authors declare no conflict of interest.

### FINANCIAL DISCLOSURES

This study was not supported by any source of finding.

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## Citation

Al-Balat, W., Hamed Youssef, N., Eldeeb, F. Treatment of Alopecia Areata using Transdermal Delivery of 5-Fluorouracil by Fractional CO2 Laser versus Intralesional Injection of 5-Fluorouracil. *Zagazig University Medical Journal*, 2024; (320-332): -. doi: 10.21608/zumj.2024.325505.3614