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Comparison of intralesional 5-fluorouracil and intralesional triamcinolone acetonide in the treatment of localized vitiligo

Maryam Tahir[1], Muhammad Khurram Shahzad[1], Tahir Hassan[1], Naima Aliya[1], Nazia Hanif[1], Asma Naz[1] and Muhammad Irfan Jamil[2]

[1]Dermatology Department, Sheikh Zayed Medical College and Hospital, Rahim Yar Khan, Pakistan
[2]Lahore General Hospital, Lahore, Pakistan

Abstract: The objective of this study was to compare the efficacy and safety of intralesional 5-fluorouracil (5-FU) and triamcinolone acetonide (TA) in the treatment of localized vitiligo. the A non-randomized control trial conducted at Sheikh Zayed Hospital, RYK, from January to June 2022 included sixty patients, aged 18-60 years, with stable vitiligo. Patients were divided into two groups: Group A received 5-FU and Group B received TA. The outcome was assessed using the Vitiligo Area Scoring Index (VASI). There were 58.3% male and 41.7% female, with an average age of 33.33±11.24 years. Baseline characteristics between the two treatment groups were comparable. At 12 weeks, treatment responses were classified as excellent (16.6%), good (16.6%), moderate (35%) and poor (31.6%), with no significant intergroup differences (p=0.203). The 5-FU group showed a more significant lesion size reduction (1.28±1.09cm²) than the TA group (0.61±1.21 cm²) (p=0.028). Adverse effects mainly included pain and erythema. Common side effects included pain and erythema. The study concludes that both intralesional 5-FU and TA are effective and safe for treating localized vitiligo, with 5-FU potentially being more efficacious in lesion size reduction and promoting repigmentation.

Keywords: Intralesional 5-florouracil, intralesional triamcinolone acetonide, vitiligo, localized vitiligo, adverse events, efficacy.

INTRODUCTION

Vitiligo is a common depigmenting disorder affecting approximately 0.5-2% of the global population, marked by well-defined patches of depigmented skin. Biopsies of the afflicted skin revealed a loss of functional melanocytes (Joge *et al.*, 2022). Lesions may manifest in a localized or widespread pattern, merging to form extensive depigmented regions. It is evident and disfiguring in those with darker skin tones. Although vitiligo is not life-threatening, it can substantially influence the affected individual's psychological well-being and quality of life (Parsad *et al.*, 2003; Yang *et al.*, 2022). The exact cause of vitiligo remains unknown. While patients often link the condition's onset to specific triggers like physical injury, illness, sunburn, emotional stress, or pregnancy, no definitive evidence supports a causal relationship with these factors. The increased frequency of autoimmune diseases in vitiligo patients and their close relatives suggests an autoimmune origin for the disorder (Alkhateeb *et al.*, 2003; Frisoli *et al.*, 2020).

Various therapeutic approaches are utilized for vitiligo treatment to promote repigmentation and halt disease progression. The primary interventions include topical corticosteroids, like clobetasol propionate, commonly used due to their anti-inflammatory properties (Binić *et al.*, 2019). To avoid inducing skin atrophy, non-steroidal alternatives, such as topical calcineurin inhibitors like tacrolimus, are recommended (Arora *et al.*, 2020). Narrowband UVB (NB-UVB) phototherapy is also an effective and well-tolerated treatment option (Silpa-Archa *et al.*, 2019). Oral glucocorticoids are suggested for rapidly progressing vitiligo, whereas topical ruxolitinib is an alternative option for nonsegmental vitiligo that affects less than or equal to 10% of the body surface area (Rosmarin *et al.*, 2020; Xie *et al.*, 2021). In cases where other treatments fail, surgical options like micro-skin grafting and tattooing can be considered. (Özdemir *et al.*, 2002; Singh *et al.*, 2010). Two intralesional agents, 5-fluorouracil (5-FU) and triamcinolone acetonide (TA), have been previously investigated for their efficacy in treating localized vitiligo.

Intralesional Triamcinolone Acetonide (TA) is effective in treating localized vitiligo due to its anti-inflammatory and immunosuppressive properties. By concentrating in affected areas, TA suppresses immune attacks on melanocytes, aiding in stabilizing and potentially reversing vitiligo. Its anti-inflammatory effects also promote a conducive environment for repigmentation (Kubelis-López *et al.*, 2021). In some cases, TA can stimulate the remaining melanocytes to produce melanin, promoting the repigmentation of the depigmented patches (Bagherani, 2012; Sharquie *et al.*, 2020; Ragab *et al.*, 2022).

5-Fluorouracil (5-FU) is a chemotherapeutic agent studied for its potential role in treating localized vitiligo. While primarily used as an anticancer drug, 5-FU has been found to possess properties that can aid in vitiligo

*Corresponding author: awesomemay30@gmail.com

management. It is thought to function by promoting melanocyte migration and proliferation, which can help restore pigmentation in affected areas. In localized vitiligo, 5-FU is often administered as an intralesional therapy, directly injected into the depigmented lesions. Some studies have shown promising results in repigmentation using intralesional 5-FU injections (Abdelshafy *et al.*, 2021; Kubelis-López *et al.*, 2021).

To date, limited evidence directly compares the efficacy and safety of intralesional 5-FU and TA in treating localized vitiligo. Given the paucity of data and the need for more effective treatments for vitiligo, a comprehensive comparison of these two intralesional agents is warranted.

MATERIALS AND METHODS

This non-randomized control trial, approved by the Institutional Review Board (IRB Approval No. 557/IRB/SZMC/SZH), was conducted at Sheikh Zayed Hospital, Rahim Yar Khan. The study employed non-probability convenience sampling for participant selection. Over six months, the study involved patients aged 18-60 with localized nonsegmental vitiligo, stable for at least six months, and without vitiligo treatment in the preceding three months. Exclusion criteria included generalized/universal vitiligo, unstable disease, hypersensitivity to 5-FU or Triamcinolone acetonide, koebnerization tendency, abnormal renal/liver functions, systemic/autoimmune diseases, pregnancy/lactation, bleeding diathesis, and immunosuppression. Data collection entailed detailed histories, including demographic information, vitiligo onset and duration, lesion distribution, and associated conditions. Ethical compliance was adhered to through written informed consent and confidentiality of patient data.

A total of 60 patients were included in the study, having thirty in each group. Group A; administered intralesional 5-FU and Group B administered intralesional Triamcinolone acetonide injections. In Group A, 0.02 cc of a 5-fluorouracil solution with a concentration of 50 mg/ml was injected intradermally at 1 cm intervals after the target area had been cleaned with a 70% alcohol swab. In Group B, the Triamcinolone acetonide injection (40 mg/ml) was diluted in distilled water to achieve a 3 mg/ml concentration and 0.1cc was then injected intradermally while keeping the 1cm spacing. For both groups, four injections were administered, each injected two weeks apart, spanning a total duration of two months.

Patients were monitored at 8 and 12 weeks, with photographs taken before and during each follow-up. The Vitiligo Area Scoring Index (VASI) was used to evaluate improvements, utilizing the following scale: 1 for specks of depigmentation (1-9% repigmentation), 2 for mostly pigmented skin (10-24% repigmentation), 3 for mixed pigmentation (25-49% repigmentation), 4 for predominantly pigmented skin (50-74% repigmentation), 5 for specks of pigmentation (75-89% repigmentation), and 6 for completely depigmented skin (90-100% repigmentation). Scores of 5-6 indicated an excellent response, 4 signified a good response, 3 represented a moderate response, and 2 or lower denoted a poor response. (Alkhateeb *et al.*, 2003; Mina *et al.*, 2018) The Grid method was employed to measure the vitiligo area before and after treatment. A transparent sheet with a 1 cm^2 grid was placed over the lesion, and the number of full and partial squares covering the lesion was counted. The total number of squares was then added and multiplied by 1 cm^2.

STATISTICAL ANALYSIS

Statistical analysis was conducted using SPSS version 26.0. Descriptive statistics summarized patient demographics and vitiligo characteristics. Independent t-tests evaluated baseline comparability between treatment groups and analyzed differences in Vitiligo Area Scoring Index (VASI) scores and lesion sizes at 8 and 12 weeks. Chi-square tests assessed the distribution of treatment responses and frequency of adverse events between groups. A p-value of <0.05 was considered statistically significant.

RESULTS

Among sixty patients, 35 (58.3%) were male and 25 (41.7%) females, with a mean age of 33.33±11.24 years. The majority, 27 (45%), fell within the 16-30 years age group. A family history of vitiligo was found in 7 (11.7%) cases. The average duration of the disease was 5.7±3.1 years, with 27 (45%) patients experiencing it for less than 5 years. No significant differences were observed regarding gender, family history, disease duration, or baseline size of localized vitiligo when comparing baseline characteristics of patients in both groups (p-value > 0.05) (table 1). The difference between the two groups was not statistically significant when comparing the VASI scores at 8 weeks (p-value 0.297) and 12 weeks (p-value 0.882) (table 2).

At 12 weeks, the overall treatment response showed: 10 patients (16.6%) with excellent results, including 7 (11.6%) from the 5-FU group and 3 (5%) from the TA group; good outcomes in 10 patients (16.6%), with 5 (8.3%) in the 5-FU group and 5 (8.3%) in the TA group; moderate progress in 21 patients (35%), with 12 (20%) in the 5-FU group and 9 (15%) in the TA group; and poor response in 19 patients (31.6%), including 6 (10%) from the 5-FU group and 13 (21.6%) from the TA group. The difference in treatment responses was not statistically significant, as evidenced by a p-value of 0.203. The initial

size of the vitiligo was comparable between the two groups (p-value 0.884). After 12 weeks of follow-up, the average lesion size in the 5-FU group was 1.1833±0.60 cm², while in the TA group, it was 1.8167±0.87 cm² (95% CI 0.2472 to 1.0196, p-value 0.002). The average reduction in size from the baseline for the two groups was 1.28±1.09 cm² and 0.61±1.21 cm² (95% CI 0.0715 to 1.2619, p-value= 0.028) (table 3).

When examining adverse events, pain and erythema emerged as the most frequent side effects for both groups. The majority of patients, with 23 in the 5-FU group and 21 in the TA group, experienced no side effects. Ultimately, the differences between the two groups were not statistically significant (table 4).

DISCUSSION

Vitiligo is a skin condition that results in white patches due to the destruction of melanin-producing cells. While there is no cure for vitiligo, several management strategies can improve the skin's appearance and prevent its spread (Kubelis-López *et al.*, 2021). These include protecting the skin from the sun, using topical treatments and phototherapy under dermatologist guidance, undergoing surgical interventions such as skin grafting or micro-pigmentation, seeking psychological support, and making lifestyle modifications (Bilal *et al.*, 2014). In this study, we aimed to compare the efficacy and safety of intralesional 5-FU and TA in treating localized vitiligo. The demographic and clinical characteristics of the patients, including gender, family history, disease duration, and baseline size of localized vitiligo, were comparable between the two treatment groups, suggesting that our results are unlikely to be confounded by these factors.

The results show the frequency of patients in both treatment groups (5-FU and TA) based on the Vitiligo Area Scoring Index (VASI) score and degree of repigmentation at 8 and 12 weeks. The 5-FU group had a higher frequency of patients with 75-89% repigmentation at 12 weeks than 5-FU group (7 vs 3 patients). Regarding the efficacy of the treatments, no statistically significant differences were observed between the two groups when comparing VASI scores at 8 weeks and 12 weeks. The treatment response at 12 weeks also showed no statistically significant differences between the groups. However, it is worth noting that the 5-FU group appeared to have slightly better outcomes, with a higher proportion of patients achieving excellent and moderate results than the TA group. The difference in treatment responses may not have reached statistical significance due to the relatively small sample size, and larger studies might be needed to explore this observation further. A study by Zohdy et al. indicated that following four intradermal sessions of 5-FU treatment, the mean size reduced from baseline 2.16±1.55cm2 to 1.7±1.42cm2. In comparison, four intradermal sessions of TA treatment resulted in a mean size reduction from baseline 2.17±1.68cm2 to 2.01±1.69cm2, with a statistically significant difference (p-value <0.05) (Zohdy *et al.*, 2019). Our findings were similar to the study mentioned earlier. Specifically, we observed that the initial size of vitiligo lesions was comparable between the 5-FU and TA treatment groups, with no significant difference found (p-value 0.884). However, after 12 weeks of treatment, the average size of lesions was significantly smaller in the 5-FU group (1.1833±0.60cm²) compared to the TA group (1.8167±0.87cm²), with a significant difference (95% CI 0.2472 to 1.0196, p-value 0.002). The reduction in lesion size from baseline was also significantly greater in the 5-FU group (1.28±1.09cm²) than in the TA group (0.61±1.21cm²), with a significant difference (95% CI 0.0715 to 1.2619, p-value= 0.028). This suggests that intralesional 5-FU may be more effective in reducing the size of vitiligo lesions compared to TA (Zohdy *et al.*, 2019). The average reduction in size from the baseline between the two groups, further supports the potential superiority of 5-FU in this regard. Another study used intradermal 5-FU injection with narrowband UV therapy to cure vitiligo. In this study, 48.3% of patients in the 5-FU group displayed outstanding repigmentation after four months of treatment, while 26.7% displayed good repigmentation. The repigmentation rate was lower in the group that only got narrowband ultraviolet therapy, with 3.3% of patients demonstrating good repigmentation and 6.7% of patients obtaining outstanding repigmentation. (Abd El-Samad *et al.*, 2012) According to Shashikiran et al., excellent repigmentation occurred in 49% of the patches treated with topical 5% 5-fluorouracil needling for vitiligo, and very good repigmentation occurred in 26% of the patches. (Shashikiran *et al.*, 2018) Khater et al. found that 43.8% of patients treated with 5-FU showed good to excellent response (repigmentation >50%). However, the excellent response was only seen in 9 (18%) patients. (Khater *et al.*, 2020) A previous study reported that treatment efficacy after intradermal 5-FU was 78.6%. (Abdelshafy *et al.*, 2021) The high efficacy was due to the difference in the operational definition of treatment response.

A study compared intralesional methotrexate and triamcinolone acetonide (TA). Results showed that intralesional methotrexate led to an excellent response in 13.3% of patients, a good response in 13.3%, a fair response in 10% and a poor response in 63.3%.

In comparison, intralesional triamcinolone acetonide resulted in excellent response in 13.3% of patients, good response in 13.3%, fair response in 16.7% and poor response in 56.7%. Their findings suggest that intralesional methotrexate and triamcinolone acetonide are effective and safe treatment options for localized

Table 1: Comparison of baseline characteristics in both groups.

Baseline Characteristics		Treatment group		P-value
		S-FU	TA	
Gender	Male	18	17	0.793
	Female	12	13	
Family History	Positive	4	3	0.500
	Negative	26	27	
Duration of disease	< 5 years	13	14	0.795
	≥ 5 years	17	16	
Mean age of patient (years)		34.30±12.06	32.37±10.48	0.510
Mean disease duration (years)		5.90±3.16	5.63±3.13	0.744
Baseline size of localized vitiligo (cm^2)		2.46±0.91	2.43±0.84	0.884

Table 2: Comparison of VASI-score between two Groups at 8 and 12 weeks.

VASI score	Treatment groups			
	5-FU		TA	
	Frequency at 8 weeks	Frequency at 12 weeks	Frequency at 8 weeks	Frequency at 12 weeks
1-9% repigmentation	7	1	8	1
10-24% repigmentation	12	5	11	12
25-49% repigmentation	8	12	7	9
50-74% repigmentation	3	5	3	5
75-89% repigmentation	0	7	1	3

Table 3: Comparison of qualitative and quantitative treatment response at 12 weeks.

Treatment response at 12 weeks	Treatment group		Total	p-value
	5-FU	TA		
Excellent	7	3	10	0.203
Good	5	5	10	
Moderate	12	9	21	
Poor	6	13	19	
Vitiligo size at baseline (cm^2)	2.46±0.91	2.43±0.84		0.884
Vitiligo size after 12 weeks (cm^2)	1.1833±0.60	1.8167±0.87		0.002
Mean decrease in size from baseline to 12 weeks (cm^2)	1.28±1.09	0.61±1.21		0.028

Table 4: Comparison of adverse effects between two groups.

Adverse effects	5-FU	TA	Total	p-value
Perilesional hyperpigmentation	3	2	5	0.500
Itching	2	3	5	0.500
Pain	5	4	9	0.500
Erythema	4	5	9	0.500
Infection	1	3	4	0.306
Necrosis/atrophy	1	3	4	0.306
Blister	1	2	3	0.500
No side effects	23	21	44	0.386

vitiligo with no significant side effect (Ragab *et al.*, 2022). Sharquie *et al.* demonstrated no significant change in the mean surface area of lesions between the baseline visit and the last follow-up visit after treatment with TA. Specifically, the mean surface area decreased from 4.56 cm^2 to 3.93 cm^2 (Sharquie *et al.*, 2020). However, the size of vitiligo was larger than our study, but results were comparable to ours with no significant decrease in lesion size.

Safety is an important consideration when evaluating treatment options for vitiligo. In our study, pain and erythema were the most commonly reported adverse events affecting 4 and 5 patients in the 5-FU and TA groups, respectively, but most patients in both groups did not experience any side effects. The differences in adverse events between the two groups were not statistically significant, indicating that both treatments have a relatively similar safety profile. Another study reported that erythema was the least common side effect, affecting only 1 patient in each group. (Zohdy *et al.*, 2019) Perilesional hyperpigmentation was reported in 3 patients in Group 5-FU and 2 in the TA group. Similarly, Zohdy et al. reported perilesional hyperpigmentation in 5 patients in the 5-FU group and none in the TA group. Atrophy was reported in 1 and 3 patients in the 5-FU and TA group, respectively, these results were also comparable to the previous study. (Zohdy *et al.*, 2019) Another previous study included 14 patients subjected to intradermal 5-FU for vitiligo. They reported that pain was the most common side effect reported by all patients, followed by hyperpigmentation in 9 patients. (Abdelshafy *et al.*, 2021)

Limitations of our study include a relatively small sample size, which may have impacted the statistical power to detect differences between the groups. Additionally, the follow-up of 12 weeks may not be sufficient to capture the long-term efficacy and safety of these treatments. Future research with larger sample sizes and extended follow-up durations may provide more insights into the comparative effectiveness and safety of intralesional 5-FU and TA in treating localized vitiligo. Future studies should explore different dosages and administration frequencies of 5-FU and TA to optimize treatment protocols and investigate the use of combination therapies involving other treatment modalities such as phototherapy, excimer laser, or topical therapies. Research should also focus on identifying factors that may predict treatment response in patients with vitiligo, which could help guide individualized treatment approaches and improve overall patient outcomes.

CONCLUSION

In conclusion, our study supports the existing literature indicating that intralesional 5-FU and TA have comparable treatment response rates and safety profiles for localized vitiligo. However, the greater reduction in lesion size observed with 5-FU suggests that it may be a more effective option for promoting repigmentation and reducing vitiligo lesion size. Further research is warranted to confirm these findings and provide more definitive guidance for clinicians managing patients with localized vitiligo.

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