Clinical Trials Study

Low-dose intralesional injection of 5-fluorouracil and triamcinolone reduces tissue resident memory T cells in chronic eczema

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Institutional review board statement: The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Shanghai University of Medicine & Health Science Affiliated Zhoupu Hospital’s Research Ethics Committee (No. 2018-C-014-M01).

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Abstract

BACKGROUND
Tissue resident memory T (TRM) cells have been reported to play a significant role in the pathogenesis and relapse of chronic eczema.

AIM
To compare the efficacy and safety of the intrallesional injection of 5-fluorouracil (5-FU) and triamcinolone (TA) with those associated with TA alone for the treatment of chronic eczema.

METHODS
A total of 168 patients were randomized to 5-FU+TA or TA groups and received a one-time intrallesional injection of 5-FU+TA or TA only. Biopsies were collected before and 2 wk after treatment for evaluation of histopathological changes. All patients were followed up monthly for up to 1 year.

RESULTS
No serious adverse event was observed in either group. Although the mean atopic dermatitis severity index scores and effective rates were comparable between the two groups after 2 wk of treatment, the relapse rate was significantly lower in the 5-FU+TA group than in the TA group. Histological examination showed significantly fewer CD8+ and CD103+ T cells but not CD4+ T cells in the 5-FU+TA group.

CONCLUSION
One-time intrallesional injection of 5-FU+TA is effective and safe for chronic eczema treatment and can further reduce the retention of T RM cells in the lesional skin and the relapse rate of chronic eczema.
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Core Tip: Chronic eczema is characterized by recurrent itchy papules and plaques with lichenification and hyperpigmentation, in which tissue resident memory T (T_{RM}) cells play a significant role. Intralesional injection of 5-fluorouracil (5-FU) and triamcinolone (TA) can effectively reduce local inflammation and recurrence in a mouse model, but no clinical study has been reported. In this study, low-dose intralesional injection of 5-FU+TA was found to effectively and safely treat the localized rash, by significantly reducing the retention of T_{RM} cells in the skin lesion, and to lower the relapse rate of chronic eczema. This combination may provide a new treatment option for chronic eczema patients with hypertrophy and localized rash.

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INTRODUCTION

Chronic eczema is a chronic inflammatory skin condition, characterized by long-course, recurrent itchy papules, and plaques with lichenification and hyperpigmentation[1-3]. Repeated scratching and irritation is the main cause of repeated delay and refractory eczema. In China, 7.5 out of every 100 people suffer from eczema[4]. Recently, tissue resident memory T (T_{RM}) cells have been suggested to play a pivotal role in the pathogenesis of chronic eczema, in addition to Th2-dominant inflammation[5]. It is reported that after 16 wk of treatment with topical corticosteroids (TCS), T_{RM} cells were still present in the tissue[6]. Further studies have confirmed that the skin lesions of dermatitis and eczema patients are dominated by CD8^+ T_{RM} cells, and these T_{RM} cells can persist for months and induce recurrent eczema[7,8].

TCS and topical calcineurin inhibitors (TCIs) are the most commonly used topical drugs for eczema treatment, and they can alleviate the localized inflammation[9]. However, some patients still suffer from repeated attacks. Oral corticosteroids and immunosuppressants have been widely used for the treatment of severe eczema. However, their long-term use can cause severe side effects, such as high blood pressure, blood glucose level, electrolyte disorders, decreased immune function, and pathogen infection. So far, Dupilumab has been approved for the treatment of moderate to severe eczema. In a phase 3 clinical trial, more than 65% of patients treated with dupilumab in combination with topical steroids achieved 75% improvement in eczema area severity index from baseline[10]. Other potential treatments for eczema such as mepolizumab and omalizumab are still under evaluation. A recent multicenter, randomized, double-blind, placebo-controlled, phase 2 clinical trial showed that 100 mg mepolizumab administered subcutaneously did not show any clinical improvement in patients with moderate to severe atopic eczema[11]. Omalizumab is a safe and relatively well-tolerated with some clinical benefits in atopic dermatitis patients[12], though its efficacy in adults is still under debate[13]. Moreover, these treatment modalities are expensive and require long-term use, which limits their clinical application.

Local intralesional glucocorticoid injection therapy has been used for decades in the treatment of localized dermatitis. Studies have shown that local injection of no more than 20 mg triamcinolone acetonide (TA) is safe and cost-effective for the treatment of localized dermatitis and other inflammatory skin diseases[14]. 5-Fluorouracil (5-FU), another common drug for intralesional injection, has been used for treating inflammatory hypertrophy in the skin as in scarring[15,16]. Our previous study has demonstrated that compared to the TA group, intralesional injection of 5-FU+TA can effectively reduce local inflammation and significantly reduce the recurrence of
Additional 5-fluorouracil reduce resident memory T cells

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Materials and Methods

Study design
This was a double-blind randomized controlled prospective study. The patients and the two dermatologists were both blinded to the group assignment. The diagnosis of chronic localized eczema was established based on the 2011 Guidelines for Eczema Diagnosis and Treatment designated by the Immunology Group, Dermatovenereology Society, Chinese Medical Association[4]. The inclusion criteria were: Age from 28–80 years and a history of chronic localized eczema lasting for > 6 mo. The exclusion criteria were: i) nullipara, pregnant, planning a pregnancy or lactating; ii) known allergies to FU or glucocorticoid; iii) treatment with any systemic corticosteroids/antibiotics/immunosuppressants in the previous 6 wk or use of topical dero
corticoids/antibiotics/antihistamines or calcineurin-inhibiting type immunosuppres
sants in the previous 2 wk; and iv) renal failure, liver dysfunction, hematological
disease, immune deficiency, systemic or local infection (including chronic obstructive
pulmonary disease patients). The study protocol conforms to the ethical guidelines of
the 1975 Declaration of Helsinki and was approved by the Shanghai University of
Medicine and Health Science Affiliated Zhongguo Hospital’s Research Ethics Committee
(No. 2018-C-014-M01). This study has been registered at http://www.chictr.org.cn/
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Patients
One hundred sixty-eight patients who visited our hospital from January 2018 to June
2019 and were diagnosed with chronic eczema with localized lesions were recruited
for the study. All patients provided signed written consent. Using a random sequence
generated by a computer program, patients were randomly assigned to two groups: a
5-FU+TA group (n = 84) and a TA (n = 84) group (Figure 1). Four patients from the 5-
FU+TA group and three patients from the TA group discontinued the study for
personal reasons.

Treatment protocol and follow-up
A one-time injection was performed for both groups. For the 5-FU+TA group, 2 mL
normal saline (Shanghai Xudong Haipu Pharmaceutical Co., Ltd.) was mixed well
with 1 mL 5-FU solution (Shanghai Xudong Haipu Pharmaceutical Co., Ltd.)
(containing 25 mg 5-FU) and 1 mL TA solution (Shanghai General Medicine Industry
Co., Ltd.) (containing 10 mg TA). Infiltration and injection were performed to allow 1
mL of the mixture into every 4 cm² of the skin lesion area. The total injection area
should be less than 32 cm² and protected from contact with water for 3 days after
injection to prevent secondary bacterial infection at the injection site. For the TA
group, 3 mL of normal saline was mixed with 1 mL of TA solution (containing 10 mg
TA). The injection method, total injection area, and course of treatment were the same
as those for the 5-FU+TA treatment group.

Follow-up was conducted 2 wk after treatment and monthly thereafter for up to 12
mo. Effectiveness was evaluated, and adverse events were recorded and photog
graphed.

Clinical data analysis
Before treatment and 2 wk after treatment, two dermatologists graded the skin lesions
of each patient independently. The evaluation of clinical efficacy referred to the atopic
dermatitis severity index (ADSI) scoring system[18]. Because chronic eczema has no
exudation, the remaining four indicators including pruritus, erythema, excoriation,
and lichenification were graded on a 4-point scale (range 0–3): none = 0 point; mild = 1
point; moderate = 2 points; and severe = 3 points. The total score for these 4 items was
≤ 12 points. An efficacy score was calculated as:

\[
\text{Efficacy Score} = \sum \frac{\text{Score of Each Indicator}}{4}
\]

Where the score of each indicator is 0, 1, 2, or 3 points.

The aim of this double-blind randomized controlled prospective clinical study was
to further evaluate the efficacy and safety of intralesional injection of 5-FU and TA for
the treatment of localized rash and management of relapse in chronic eczema patients
and to explore the potential underlying mechanism.
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168 patients underwent randomization

Assigned to the 5-FU+TA group (n = 84)

Dropped out (n = 2)

Completed the treatment (n = 82)

Assigned to the TA group (n = 84)

Completed the treatment (n = 84)

Dropped out (n = 3)

Completed the study (n = 81)

Completed the study (n = 80)

Figure 1 Randomization and allocation of patients to the study groups. 5-FU: 5-fluorouracil; TA: triamcinolone.

Efficacy score = (score before treatment – score after treatment)/ score before treatment × 100%

The efficacy criteria were: cure, score > 90%; excellent response, score 61%–90%; good response, score 20%–60%; and poor or nonresponse, score < 20%.

Effectiveness percentage = (number of cured patients + number of patients with excellent response)/ total number of patients × 100%

The patients were followed up for 1 year, and the number of patients who relapsed was recorded.

Relapse rate = number of patients with eczema relapse/ total number of effective patients (cured patients + patients with excellent response) × 100%

Evaluation of adverse events

Routine blood tests and liver and kidney function tests were performed before and 2 wk after treatment. We also monitored and recorded the events of local infection, skin atrophy, pigmentation, etc. after treatment and during the 1-year follow-up.

Histopathological examination and immunohistochemical staining

To investigate the histopathological changes and the infiltration of T_{RM} cells and other immune cells after treatment of chronic localized eczema, we collected biopsy specimens at the lesion site from 15 patients in each group before and 2 wk after treatment.

For staining of lesional tissue with hematoxylin and eosin (HE), fixed tissues were embedded in paraffin and cut into 5 μm thin sections, followed by staining with HE.

For immunohistochemical staining, the lesional tissue sections were washed in phosphate-buffered saline and then boiled in EDTA for antigen retrieval, followed by 3% hydrogen peroxide incubation and 5% bovine serum albumin blockade. Tissue sections were incubated with primary antibodies against CD4 (1:100, Shanghai Jiehao Biotechnology Co., Ltd., Shanghai, China), CD8 (1:100, Shanghai Jiehao Biotechnology Co., Ltd.,), and CD103 (1:150, Abcam, Cambridge, UK). After incubation with a secondary antibody, staining results were observed under a microscope (Olympus, Tokyo, Japan). The images were recorded for further analysis. Cell counts were performed blindly on randomly selected histological images at ×100 magnification (High power field).

Statistical analyses

The data were analyzed using PASW software, version 22 (IBM Corporation, Armonk, NY). The graphs were plotted using GraphPad Prism, version 8.00 (GraphPad Software, Inc., San Diego, CA). Disease duration was compared between groups using the Mann–Whitney U test. Independent t-tests were used to compare the patients’ ages, ADSI scores, and T-cell counts. The chi-squared test and Fisher’s exact test were used to determine statistical differences between the groups in relation to sex, the
anatomical site treated, the effective rate of treatment, and the recurrence rate. A two-tailed P value < 0.05 was considered statistically significant. Unless otherwise specified, data are presented as mean ± SD.

RESULTS

Patient characteristics
The baseline demographic and clinical characteristics of patients in the two groups are summarized in Table 1. The age, sex, number of anatomical sites treated, and disease duration did not differ significantly between the groups (P > 0.05 for all).

Clinical outcomes
The mean ADSI scores of patients who complete the treatment and evaluation of clinical efficacy before treatment were 7.89 ± 0.89 in the 5-FU+TA group and 7.68 ± 1.02 in the TA group (P = 0.154). Two weeks after treatment, pruritus was alleviated significantly according to the patients, and the color of erythema became lighter in both groups. A small amount of scales was found in 23 out of 84 patients (27.38%) in the TA group (Figure 2). The mean ADSI scores at 2 wk after treatment for the 5-FU+TA group and TA group were 1.55 ± 0.82 and 1.74 ± 0.94, respectively. The ADSI scores for both groups were significantly lower than those before treatment for the same group (P < 0.001 for both), and there was no significant difference between the two groups (t = -1.383, P = 0.168; Figure 3A). Interestingly, at the 1-year follow-up, relapse had occurred in 4 patients (5.00%) in the 5-FU+TA group and 25 patients (30.86%) in the TA group (c² = 18.232, P < 0.01, Figure 3C).

Adverse events
Six patients in the 5-FU+TA group and five patients in the TA group had local pruritus after injection, which resolved without further treatment. During the follow-up, local pigmentation was observed in both groups, and it gradually improved over time. No obvious skin atrophy, redness, swelling, heat, pain, or other symptoms of infection were noted in either group. There were no adverse reactions such as leukopenia, anemia, and thrombocytopenia in either group during the 1-year follow-up.

Intralesional injection of 5-FU+TA reduced local retention of CD103+ memory T cells
To explore the mechanism by which 5-FU and TA reduced the relapse rate of chronic eczema, we investigated differences in T-cell infiltration in the local skin lesions of patients from both groups before treatment and 2 wk after treatment by HE and immunohistochemical staining. The results showed that the lesional skin was infiltrated with lymphocytes and other inflammatory cells in the epidermis before treatment. A number of CD4+, CD8+, and CD103+ T-cell infiltration was observed in both groups with no significant differences (P = 0.914, 0.945, 0.988, respectively; Figure 4A). Two weeks after treatment, the CD4+, CD8+, and CD103+ T-cell counts for the two groups were significantly less than before treatment (all P < 0.001, n = 15 for each group). Although no significant difference was observed in the number of CD4+ T cells between the two groups (P = 0.355) at 2 wk after treatment, the numbers of CD8+ and CD103+ T cells in the skin lesions were significantly less in the 5-FU+TA group than in the TA group (P = 0.025, P < 0.001; Figure 4B). In some skin lesions from the 5-FU+TA group, no inflammatory cell infiltration was observed.

DISCUSSION

Chronic eczema recurs frequently, and its treatment has always been challenging. Once the skin lesions become hypertrophic, the penetration of conventional topical drugs such as TClis is decreased. Although intralesional corticosteroid has been proven effective for localized dermatitis, long-term or high-dose application of TCI treatment may cause skin atrophy, telangiectasia, increased vellus hair, systemic absorption, pricking, and burning sensations[3,19]. Intralesional 5-FU has been also used for
Table 1 Patient demographic and baseline disease characteristics

|                              | Patients underwent randomization (n = 168) | Patients completed study (n = 161) |
|------------------------------|------------------------------------------|-----------------------------------|
|                              | 5-FU + TA (n = 84)                       | TA (n = 84)                       | 5-FU + TA (n = 80) | TA (n = 81) | P     |
| Age (mean ± SD), yr          | 54.39 ± 14.31                           | 56.12 ± 14.82                    | 0.643              | 54.74 ± 14.26 | 55.60 ± 12.56 | 0.683 |
| Range                        | 28-74                                    | 28-79                            | 28-74              | 29-79       |
| 28-45                        | 36.17                                    | 38.48                            | 0.120              | 36.27       | 38.16 | 0.256 |
| 46-60                        | 53.48                                    | 53.41                            | 0.962              | 53.50       | 53.41 | 0.950 |
| 61+                          | 67.27                                    | 66                               | 0.258              | 64.56       | 66.13 | 0.416 |
| Sex, n (%)                   |                                          |                                  |                    |             |       |       |
| Male                         | 59 (70.24)                               | 57 (67.86)                       | 56 (70)            | 55 (67.90) |
| Female                       | 25 (29.76)                               | 27 (32.14)                       | 24 (30)            | 26 (32.10) |
| Anatomical sites treated, n (%) |                                          |                                  |                    |             |       |       |
| Trunk                        | 23 (27.38)                               | 22 (26.19)                       | 0.862              | 23 (28.75) | 22 (27.16) | 0.822 |
| Limb                         | 58 (69.05)                               | 61 (72.62)                       | 0.611              | 54 (67.50) | 58 (71.60) | 0.571 |
| Neck                         | 3 (3.57)                                 | 1 (1.19)                         | 0.613              | 3 (3.75)   | 1 (1.24) | 0.604 |
| ADSI score (mean ± SD)       | 7.72 ± 1                                 | 7.68 ± 1.02                      | 0.468              | 7.71 ± 1   | 7.87 ± 0.90 | 0.278 |
| Disease duration, yr (range) | 4 (1-24)                                 | 4 (1-30)                         | 0.944              | 3 (1-24)   | 3 (1-30) | 0.925 |

FU: 5-fluorouracil; TA: triamcinolone; ADSI: atopic dermatitis severity index

Figure 2 Representative images of localized chronic eczema lesions before and 2 wk after treatment. Skin lesion of a patient in the intralesional 5-FU+TA treatment group (A) at baseline and (B) 2 wk after 5-FU+TA treatment. Skin lesion of a patient in the intralesional TA treatment group (C) at baseline and (D) 2 wk after TA treatment. 5-FU: 5-fluorouracil; TA: triamcinolone.

Additional 5-fluorouracil reduce resident memory T cells
Additional 5-fluorouracil reduces resident memory T cells

Figure 3 Clinical responses of the localized lesions of chronic eczema to intralesional treatment with low-dose 5-FU+TA and TA at 2 wk after treatment. (A) Mean atopic dermatitis severity index (ADSI) scores before and 2 wk after treatment. (B) A number of patients who achieved cure, excellent response, and good response 2 wk after treatment with 5-FU+TA or TA. (C) A number of patients who experienced relapse after treatment with 5-FU+TA (n = 4) or TA (n = 25) during 1-year follow-up. (P < 0.01). 5-FU: 5-fluorouracil; TA: triamcinolone.

The first to observe the effect of 5-FU+TA on chronic eczema through intralesional injection.

To the best of our knowledge, there has been no study investigating the effectiveness of corticosteroids for eczema treatment through intralesional injection. A previous study investigated the use of 0.05% fluticasone propionate cream or 0.005% fluticasone propionate ointment given once or twice daily to eczema patients for 1 mo and continued twice weekly thereafter. In that study, the relapse rate at the 16 wk follow-up was 19% for the 0.05% fluticasone propionate cream group and 40% for the 0.005% fluticasone propionate ointment group. For the placebo group, the average relapse time was 6 wk, and the relapse rate was 64% [20].

In the present double-blind randomized study, local injection using 5-FU+TA or TA only was applied, and the patients were followed up for up to 1 year. Our data demonstrate that a one-time intralesional injection of TA in combination with 5-FU could successfully treat the localized rash of chronic eczema. Most importantly, the relapse rate in the 5-FU+TA group was significantly lower than that in the TA group (4.9% vs 31.64%), and also much lower than the rate in the previously mentioned study, demonstrating that 5-FU+TA treatment via intralesional injection can significantly reduce the recurrence of eczema.

The aggravating factors for adult eczema include environmental factors, sweating, physical irritation (including scratching), microbes, stress, and food [21]. Our study was a double-blind randomized controlled prospective study, and all participants were outpatients from our hospital with similar living environments and eating habits. We did not find statistically significant differences in age, sex, anatomical sites treated, or the treatment period among the groups.

There is a common concern of the potential adverse reaction of intralesional TA and 5-FU, such as infertility, skin atrophy, and telangiectasia. For the treatment of keloid scars, it is suggested that 5-FU (maximum 90 mg each injection) + TA treatment resulted in a lower incidence of skin atrophy and telangiectasia than treatment with TA alone (10-40 mg TA single injection) [22,23]. The common dosage range of 5-FU is 45-50 mg/mL, and each injection volume is less than 2 mL, with more than 3 sessions.
Figure 4 Histopathology and immunohistochemistry of localized lesions of chronic eczema to intralesional treatment with 5-FU+TA and TA before and 2 wk after treatment. (A) Representative histologic images of biopsy specimens from localized lesions of chronic eczema were collected before and at 2 wk after treatment. Tissue samples (n = 15 for each group) were stained with HE and antibodies against CD4, CD8, or CD103 to detect T-cell infiltration in the lesional skin. (B) CD4⁺, CD8⁺, and CD103⁺ T cell counts were quantified in high-power field images of lesions biopsied before and 2 wk after treatment. Blue points: 5-FU + TA group; Red points: TA group. *P < 0.05, **P < 0.01. 5-FU, 5-fluorouracil; TA, triamcinolone.

In this study, 25 mg 5-FU and 10 mg TA were used intralesionally once for the treatment. Compared with the dosage for keloid treatment, our dosage of 5-FU and TA is relatively low. Laboratory tests after 2 wk of treatment showed no abnormal results for blood and liver and renal function. Similarly, no such adverse events were
observed during the 1-year follow-up. Moreover, the dosage of TA is half of the maximum safe dose reported in a previous study (20 mg) for the treatment of localized dermatitis[14]. No adverse reactions such as skin atrophy or telangiectasia were observed in this study, suggesting that the combination of 5-FU and TA at these dosages was safe for chronic eczema treatment. 5-FU and TA both have an immune suppressive effect, which requires attention regarding the chance of local infection. Patients were informed about the risk of bacterial contamination. No local infection was observed in either group during the follow-up. In clinical practice, topical antibiotics such as Mupirocin could be prescribed for infection prevention.

**Conclusion**

In summary, our study demonstrated that intralesional injection of 5-FU+TA can effectively and safely treat the localized rash of chronic eczema and significantly reduced the retention of T<sub>RM</sub> cells in the skin lesion. This combination may provide a new treatment option for chronic eczema patients with epidermis hypertrophy and localized rash.
while the relapse rate was significantly lower in the 5-FU+TA group than in the TA group. Histological examination showed significantly fewer CD8+ and CD103+ T cells but not CD4+ T cells in the 5-FU+TA group.

Research conclusions
5-FU+TA can effectively and safely treat the localized rash of chronic eczema and significantly reduce the retention of T_{res} cells in the skin lesion.

Research perspectives
Low-dose intralesional injection of 5-FU+TA may be a new treatment option for chronic eczema patients with epidermis hypertrophy and localized rash.

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