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ORIGINAL RESEARCH

Cladribine Ameliorates Imiquimod Induced Murine Psoriasiform Dermatitis

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Background: Significant progress has been made in understanding the mechanisms of psoriasis, particularly the role of the interleukin (IL)-23/T-helper (Th) 17 axis, leading to novel, targeted therapies. However, many patients develop resistance to treatment over time. Thus, exploring new therapeutic strategies for severe refractory psoriasis remains crucial.

Objective: To investigate the effect of cladribine on imiquimod induced psoriasiform dermatitis in mice.

Methods: We established an imiquimod (IMQ)-induced psoriasiform dermatitis mouse model to investigate cladribine's effects on skin immune cells. Mice were allocated to five groups: Control, IMQ, High-dose cladribine (30mg/kg), Low-dose cladribine (20mg/kg), and Methotrexate. We assessed cumulative scores, skin pathology, immunohistochemistry, flow cytometry, and serum cytokines. We also studied cladribine's long-term efficacy by reapplying IMQ for a second round (7 days) after five half-lives of cladribine.

Results: Cladribine significantly ameliorated symptoms and pathological features of IMQ-induced psoriasis in both high and low-dose groups, with efficacy comparable to methotrexate. Cladribine dose-dependently reduced Th17 and Th1 cell frequencies in psoriatic skin, along with associated cytokines. High-dose cladribine demonstrated sustained inhibition of IMQ-induced psoriasis.

Conclusion: These findings indicate that cladribine can ameliorate imiquimod-induced psoriasiform dermatitis in mice, exhibiting a dose-dependent and sustained therapeutic effect.

Keywords: cladribine, imiquimod-induced murine model, psoriasis

Introduction

Psoriasis is a chronic autoimmune dermatological disorder characterized by white scales and clearly demarcated erythematous plaques.[1] Immunological and genetic studies have identified IL-17 and IL-23 as key drivers of psoriasis pathogenesis.[2] Immune targeting of these cytokines and of TNFα by biological therapies has revolutionized the care of moderate to severe chronic plaque disease.[3] However, challenges such as adverse effects, treatment resistance, high costs, and variability in response among individuals persist.[4,5] Refractory psoriasis to systemic therapies can be due to non-adherence but can also be due to ineffective dosing, development of anti-drug antibodies (ADAs), and severe disease that necessitates multiple drugs.[6,7] Patients exhibiting multi-drug resistance, defined as those who have failed more than four biologic therapies with minimal or no therapeutic benefit, pose a growing challenge for clinicians.[8] The future of psoriasis treatment holds promise for improved outcomes.[9]

Cladribine (2-Chlordeoxyadenosine, 2-CdA), a purine nucleoside analog with immunosuppressive properties, was rationally designed to target the biochemical pathways that result in lymphocyte depletion, particularly in the context of adenosine deaminase deficiency.[10,11] T cells can accumulate the drug 2-CdA, leading to both CD4+ and CD8+ lymphocytopenia, and the duration of this effect can be substantial.[12] 2-CdA, approved by the FDA for the treatment of hairy cell leukemia, has garnered clinical data suggesting its potential value in multiple sclerosis (MS) and other autoimmune disorders, such as autoimmune hemolytic anemia, rheumatoid arthritis,

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systemic lupus erythematosus (SLE) and Sjogren's syndrome.[13] Our group has successfully applied 2-CdA in the treatment of xanthoma disseminatum with encouraging outcomes and a satisfactory toxicity profile.[14,15]

Anecdotal evidence has indicated that 2-CdA may serve as a therapeutic agent for patients with psoriasis (Table 1).[11,12,16,17] This is the first study aimed to evaluate the influence of 2-CdA on mouse model to lay a stronger foundation for application of this drug. Imiquimod (IMQ), a toll-like receptor 7/8 agonist, induces psoriasis-like skin lesions at the granular level in mice that closely resembles human psoriasis, critically dependent on the IL-23/IL-17 axis.[18] Therefore, we sought whether 2-CdA has the capability to rescue psoriasis using an IMQ mouse model, as well as the long-term efficacy.

Materials and Methods

Animals

Eight-week-old, C57BL/6J (B6) mice were purchased from Charles River (Beijing, China). The mice were adapted for one week before the start of the experiments. All mice were housed in a specific pathogen-free environment. Ethical approval for the study was granted by the Ethics Committee of the Institutional Animal Care and Use Committee (IACUC) of Tsinghua University. All experimental manipulations were conducted in compliance with the Institutional Guidelines for the Care and Use of Laboratory Animals.

IMQ Mouse Model

IMQ cream (5%) (Aldara^{TM}; 3M Health Care, Loughborough, UK) was used to induce psoriasis-like skin symptoms in mice. The hair on the backs of the C57BL/6J (B6) mice was shaved using an electric shaver, after which they were treated with a daily topical dose of 62.5 mg IMQ cream for 7 days. The initiation of psoriasis by IMQ in mice was designated as day 1. From day 1 to day 9, B6 mice were injected i.v. with 20mg/

Table 1 Literature Review of 2-CdA Application in Patients With Psoriasis

Study	Patient Numbers	Age	Sex	Primary Diagnosis	Psoriasis Severity	Treatment	Response	Safety
Ilyas[12]	1	73	Male	Hairy cell leukemia for 20 years	90% BSA (MTX 10mg/week, minimal improvement)	1-week intravenous infusion of 2-CdA for 4 weeks	Complete remission, with only psoriatic nail changes remaining, less than 1% BSA involvement following up for 4 years	Pancytopenia and fever, which eventually resolved without serious complications
Zinzani[16]	1	47	Male	Hairy cell leukemia	Symmetrical areas of involvement at the elbows, knees, and the scalp (topical glucocorticoids and keratolytic agents and UV irradiation ineffective)	A dose of 0.1mg/kg daily by continuous infusion for 7 days	2 weeks after, complete clearance of psoriatic lesions for 8 months, after which the psoriatic lesions slowly reappeared	\
Eibschutz[11]	1	43–67	5Fand2M	Psoriatic arthritis for 3–21 years	\	Oral 2-CdA at weekly dosages of 0.3–0.45mg/kg for 12 weeks, followed by monthly maintenance therapy	One patient dropped because of perceived lack of efficacy, 4 of 6 had improved joint disease, and 5 of 6 had improved psoriasis	T and B Lymphocytes depleted; well tolerated; Herpes zoster
Valencak[17]	1	58	Female	Gastric marginal zone B-cell lymphoma of MALT type	Chronic plaque psoriasis	Intravenous treatment with 0.12mg/kg per day of 2-CdA over 5 days every 4 weeks for six cycles	Improved significantly after 2 months of 2-CdA administration; complete remission after 3 months following up for 34 months	A long-term T cell depletion

Abbreviations: BSA, body surface area; MTX, methotrexate; MALT, mucosa-associated lymphoid tissue; 2-CdA, cladribine.

kg or 30mg/kg 2-CdA daily for 9 days.[19,20] The control group was intragastrically administered with 1mg/kg MTX (Shanghai Sine Pharmaceutical Laboratories Co., Ltd., Shanghai, CN) for 9 days.

Scoring Severity of Skin Inflammation

To assess the severity of inflammation of the back skin, an objective scoring system was developed based on the clinical Psoriasis Area and Severity Index (PASI), with the exception that the affected skin area is not factored into the overall score. Two investigators were involved in the severity scoring. Erythema, scaling, and thickening were each scored independently on a 0 to 4 scale: 0 indicated none; 1 indicated mild; 2 indicated moderate; 3 indicated severe; and 4 indicated very severe. The total score, calculated as the sum of erythema, scaling and thickening scores, served as a measure of the severity of inflammation, with a scale ranging from 0 to 12.

Histology

At the end of the experiment, dorsal skin samples were fixed in 4% formaldehyde solution, subsequently embedded in paraffin, and then sectioned into 5 μm slices using a microtome. Tissue slices (5μm) were processed according to standard histological procedures and stained with hematoxylin and eosin (H&E) for pathological observation by light microscopy (Nikon Eclipse E100). Epidermal thickness, a recognized end-point for measuring the severity of psoriasis, was accurately measured with ImageJ software (National Institutes of Health, Bethesda, MD, United States).

Immunohistochemistry

Anti-rabbit proliferating cell nuclear antigen (PCNA) (GB11010, 1:500, Wuhan Servicebio Technology Co., Ltd., Wuhan, CN) was utilized for immunostaining of skin samples from the back-skin lesions. Subsequently, the staining was evaluated, and photomicrographs were captured using a light microscope (Nikon Eclipse E100, Japan). Five randomly selected high-magnification (400x) visual fields were employed to quantify the number of $PNCA^{+}$ cells within the epidermis. Semi-quantitative image analysis was conducted independently by two researchers using Image-Pro Plus 6.0 (Media Cybernetics, USA).

Flow Cytometric Analysis

For flow cytometric analysis, lesional tissue were excised and dissected into small pieces. Skin cell suspensions were prepared subsequent to enzymatic digestion with collagenase I (1 mg/mL, Invitrogen) for 2 h at 37 °C. The digestion was followed by mechanical dissociation of the tissue using 70 μm cell strainers. The resulting single-cell suspensions were labeled with the targeted antibodies, including anti-mouse CD4, anti-mouse CD3, anti-mouse IFN-γ, and anti-mouse IL17A (Biolegend, USA). Flow cytometric analysis was performed. A minimum of 10,000 events were analyzed utilizing the FACSCalibur system (Becton Dickinson, San Jose, CA, USA) with CellQuest Pro software.

Assay of Cytokine Production

To quantify cytokine levels, mouse serum was collected 24 h post the final drug administration and stored at - 70 °C until analysis. The concentrations of TNF-α, IFN-γ, IL-17, IL-2, IL-4, IL-6, and IL-10 in the mouse serum were determined using the mouse TNF-α, IFN-γ, IL-17, IL-2, IL-4, IL-6, and IL-10 (Abcam, Shanghai, CN) ELISA kits. The ELISA assays were conducted in accordance with the manufacturer's instructions.

Statistical Analysis

All data were presented as mean ± standard deviation calculated from at least three independent experiments. Differences between groups were analyzed using one-way ANOVA. Values of $P < 0.05$ was considered to be statistically significant. GraphPad Prism 10 was utilized for data analysis and creating charts in this study.

Results

Cladribine Improved the IMQ-Induced Psoriasiform Dermatitis

To examine the protective effects of 2-CdA in the development of IMQ-induced psoriasis in mice, mice were intravenously administered with 2-CdA (20mg/kg or 30mg/kg) for 9 days after IMQ application (Figure 1A). The cumulative score, derived from the individual symptom scores, was based on the severity of erythema, scaling, and thickness (Figure 1B). These symptoms were significantly ameliorated in mice treated with both high or low-doses of 2-CdA (Figure 1C). A significant reduction in scores was observed in both the high-dose and low-dose 2-CdA groups compared to the IMQ group; however, no significant differences were noted between the high-dose or low-dose 2-CdA groups (Figure 1D).

Histology of Skin Lesions in Mice With IMQ-Induced Psoriasis Treated With Cladribine

To validate the suppressive effects of 2-CdA, histopathological examination of dorsal skin samples was performed using standard H&E staining and PCNA immunostaining. The IMQ group, exhibiting psoriasis-like skin lesions, displayed characteristic histopathological changes associated with psoriasis, including inflammatory cell infiltration, parakeratosis, and hyperkeratosis, in contrast to the control group (Figure 2A). After a 9-day treatment period, both 2-CdA and MTX treatments significantly attenuated psoriasis-like pathological changes (Figure 2A). Both the high or low-dose 2-CdA treatment significantly reduced the thickness of the epidermal layer (55.2 ± 4.14μm in the high-dose 2-CdA group, 66.6 ±2.41μm in the low-dose 2-CdA group vs 178 ± 14.83μm in the IMQ group, $p < 0.0001$) (Figure 2B). PCNA, a marker of DNA synthesis in cells, predominantly indicates the proliferation status indicator of keratinocytes. Following 2-CdA therapy, there was a significant decrease in the number of mitotically active cells within the basal layer, suggesting that 2-CdA treatment might inhibit IMQ-induced proliferation of keratinocytes (Figure 2C). Additionally, the high-dose 2-CdA group exhibited a lower number of $PCNA^+$ cells in the epidermis compared to the low-dose 2-CdA group (Figure 2C).

Decreased Frequency of Th17 and Th1 Cells in IMQ-Induced Psoriatic Skin Lesions Treated With Cladribine

Considerable data support the notion that both Th17 and Th1 cells are increased within the lesional skin of psoriatic patients.[21,22] To ascertain the proportions of Th17 and Th1 cells in the dorsal skin, skin cells were stained for IL-17A, CD4, CD3 and IFN-γ, and subsequently analyzed using flow cytometry (Figure 3A). IMQ-treated mice exhibited elevated percentages of CD4 $^+$IL-17A$^+$ T cells and $CD3^+CD4^+$IFN-γ^+ T cells when compared with control group (Figure 3B). In contrast, treatment with both high-dose and low-dose 2-CdA significantly reduced the frequency of CD4 $^+$IL-17A$^+$ T cells and $CD3^+CD4^+$IFN-γ^+ T cells compared with the IMQ group (Figure 3B). Interestingly, the high-dose 2-CdA group has relatively lower percentages of Th17 and Th1 cells compared with the low-dose 2-CdA group (Figure 3B).

Inhibition of IMQ-Induced Inflammatory Cytokine Levels by Cladribine

To investigate the impact of 2-CdA on a spectrum of cytokines associated with psoriasis, we quantified the serum levels of these inflammatory mediators in mice using ELISA. As shown in Figure 4, the expression levels of the Th1 cytokines (TNF-α, IFN-γ, and IL-2) and Th17 cytokine (IL-17) in the serum showed marked inhibition in both the high or low-dose 2-CdA group and MTX group, compared to the IMQ group. Conversely, the secretion of Th2 associated cytokines (IL-4 and IL-10) was increased in both the high-dose 2-CdA group and MTX group, compared to the IMQ group (Figure 4). Finally, the level of secreted IL-6 was significantly lower in both the high-dose 2-CdA group and MTX group, compared to the IMQ group (Figure 4).

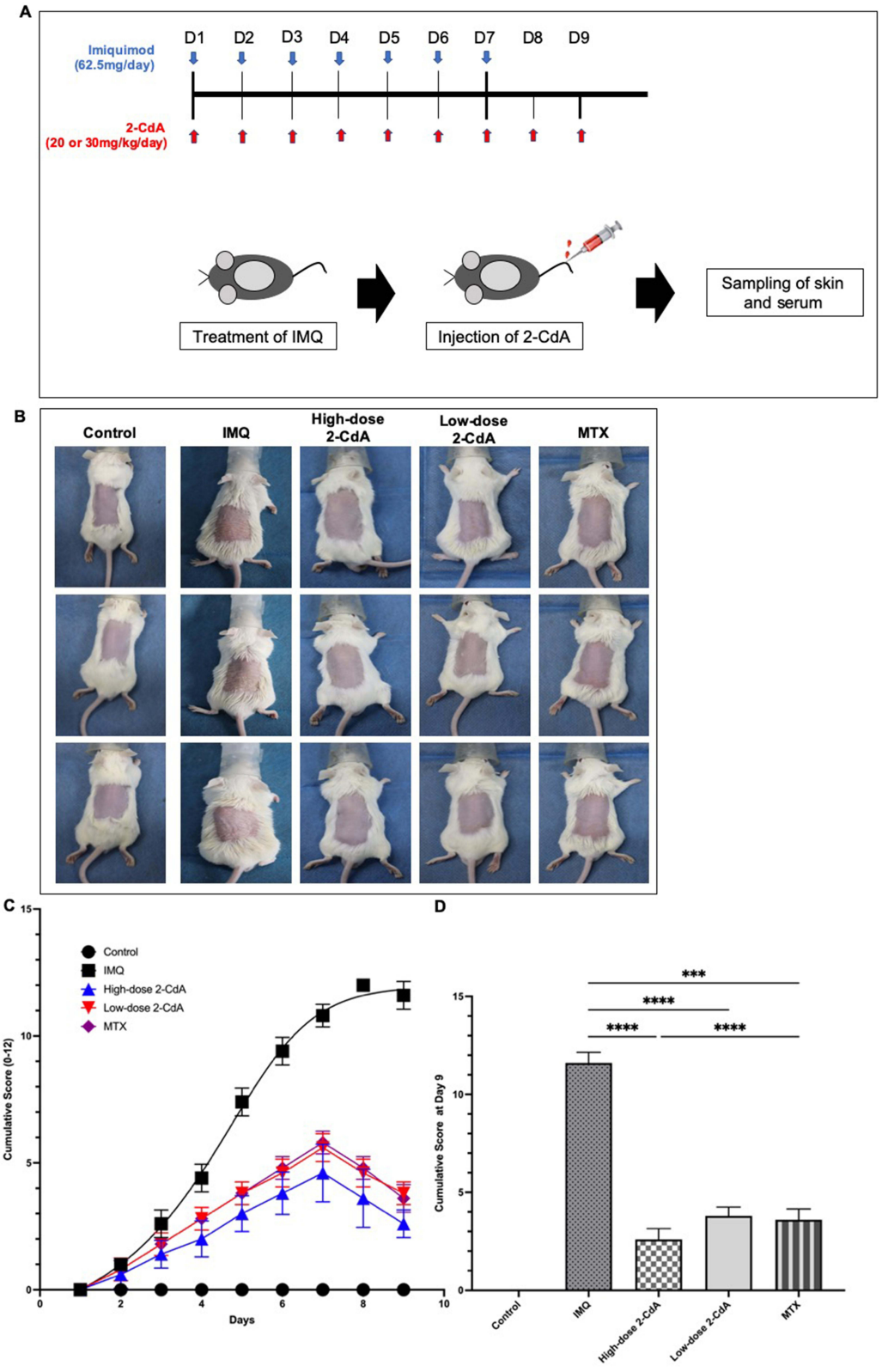

Figure 1 Effects of 2-CdA on IMQ-induced psoriasis-like skin inflammation in mice. (**A**) Mice were intravenously (i.v.) injected with 2-CdA for 9 days after initiation of the topical application of IMQ. (**B**) Photographs are representative of mice dorsal skin. (**C**) Time-course of cumulative score. Several representative symptoms were measured by a cumulative score (erythema plus scaling plus thickness). (**D**) The cumulative scores on day 9 were statistically assessed. The data are expressed as average values ± SD, n=5, n represent the number of mice in each group. *** P<0.001, **** P<0.0001.

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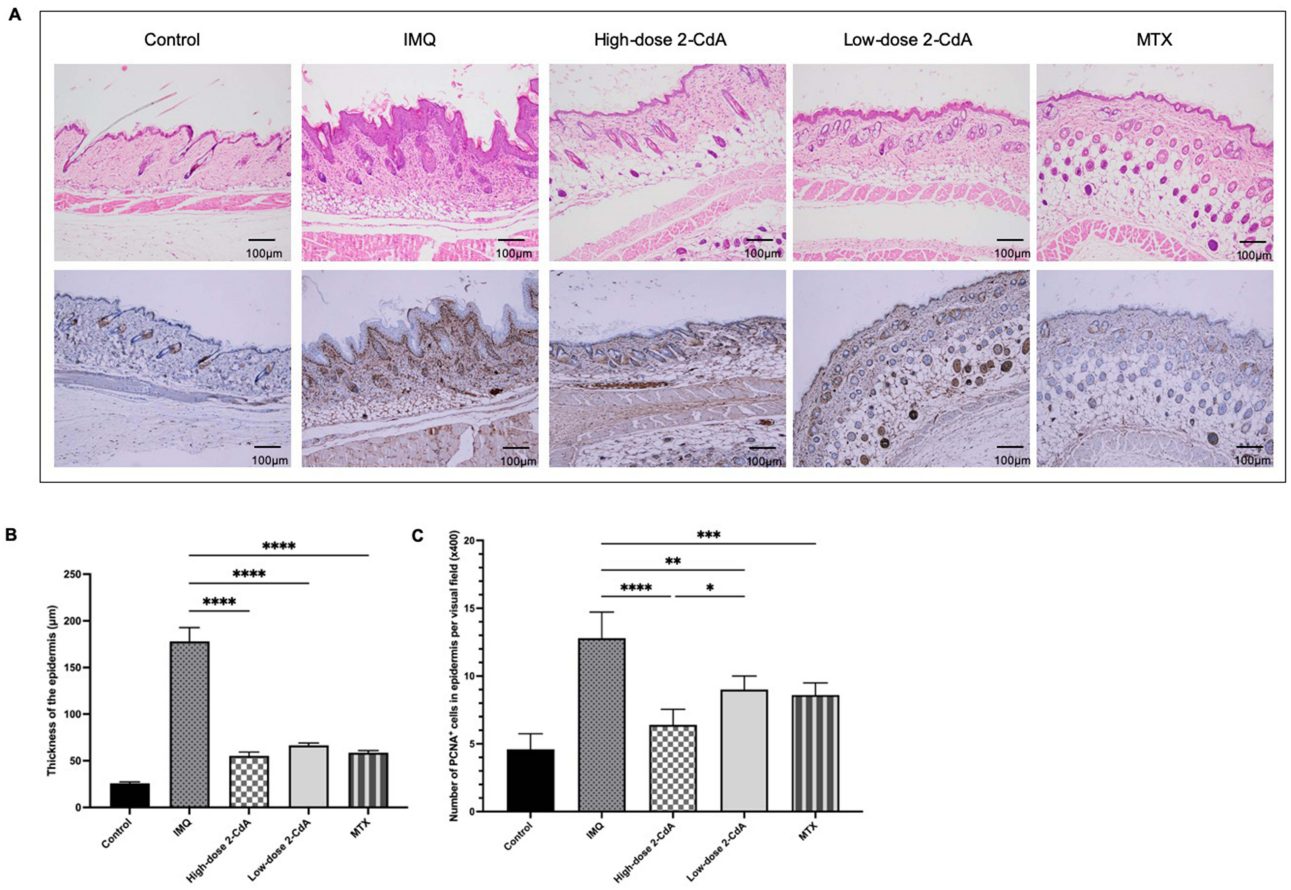

Figure 2 Histological analysis of skin lesions. (**A**) Typical H&E sections and PCNA staining of back lesions on day 9 (x100), scale bar= 100μm for all panels. (**B**) The thickness of the epidermis in the back lesions was measured. (**C**) The PCNA-positive cells in dorsal lesions were statistically assessed. The data are expressed as average values ± SD, n=5, n represent the number of mice in each group. **P*<0.05, ***P*<0.01, *** *P*<0.001, **** *P*<0.0001.

The Long-Term Efficacy of Cladribine on IMQ-Induced Psoriasis

To explore the long-term efficacy of cladribine on IMQ-induced psoriasis, we performed second round of IMQ application for 7 days after five drug half-lives of cladribine (5 days)[23] when all skin symptoms was normalized (Figure 5A). As shown in Figure 5B and C, both previous high-dose 2-CdA and MTX treatments could significantly improve IMQ-induced psoriasis compared with the IMQ group which was not exposed to any of the drugs, however, low-dose 2-CdA did not have obvious long-term efficacy on IMQ-induced psoriasis.

Discussion

Psoriasis is recognized as a chronic immune-mediated inflammatory skin disorder, with a substantial body of evidence indicating that activated T lymphocytes play a crucial role in the development of psoriasis.[24] Theses T cells are categorized into two main subtypes: conventional adaptive T cells (such as $CD4^+$ T cells, $CD8^+$ T cells, T_{RM} cells, and Treg cells) and innate-like T cells (such as NKT cells, MAIT cells, and γδ T cells). Collectively, these cells are central to maintain the inflammatory cycle characteristic of psoriasis development.[25–29]

Topical application of imiquimod to the mouse ear or back skin results in a phenotype that shares many characteristics with many human psoriasis. This model closely mimics human plaque-type psoriasis, exhibiting features such as skin erythema, thickening, scaling, epidermal alterations (acanthosis, parakeratosis), and neo-angiogenesis, as well as an inflammatory infiltrate comprising T cells, neutrophils, and dendritic cells.[18] However, there is ongoing debate regarding the cytokine and cell infiltrate environment in imiquimod-induced inflammation compared to naturally occurring psoriasis.[30] The cytokine profiles of these IMQ-induced skin

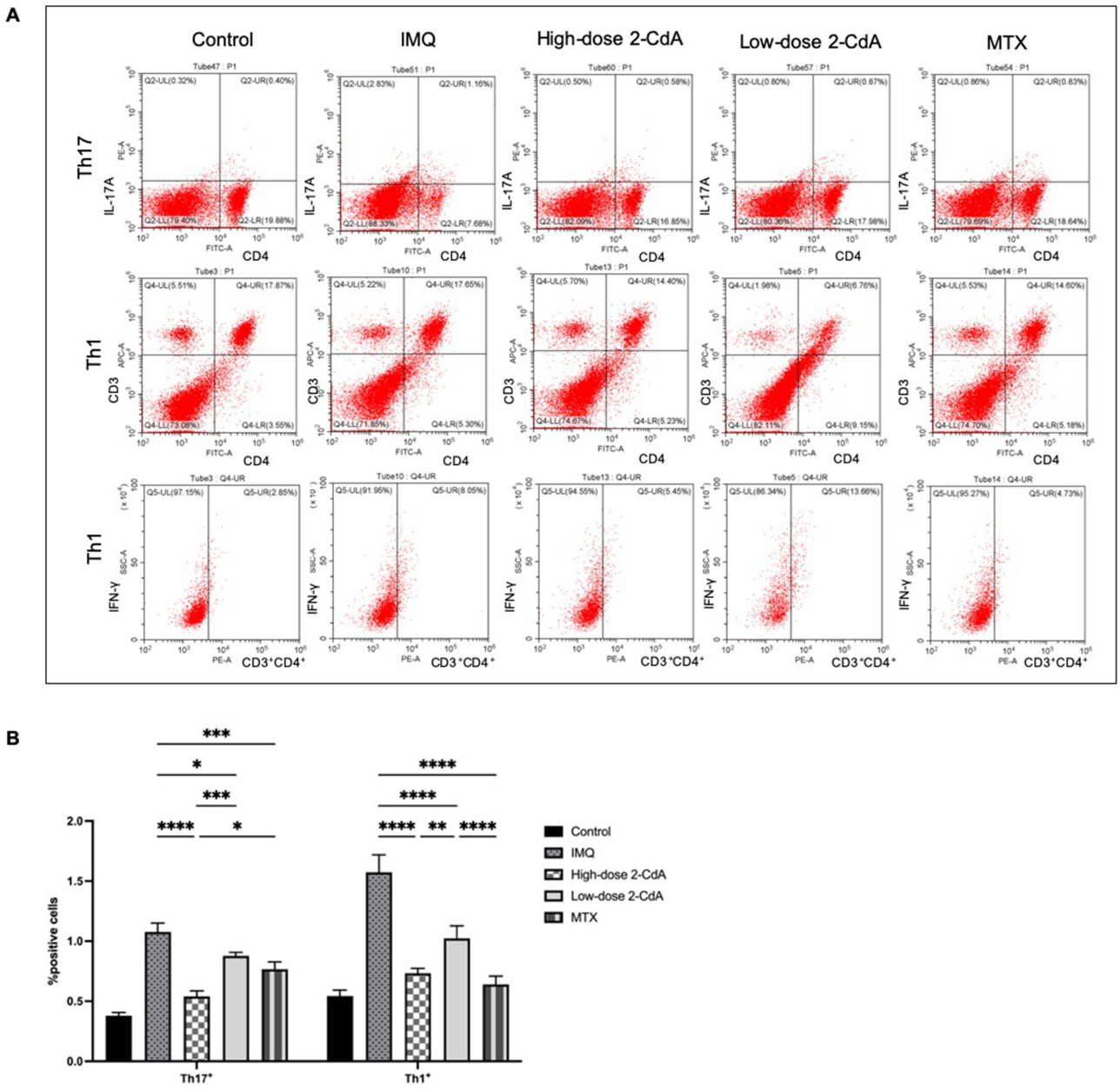

Figure 3 Proportions of Th17 and Th1 cells in skin lesions determined by flow cytometry. (**A**) $Th17^+$ cells were selected and sorted according to CD4 and IL-17A status, and $Th1^+$ cells were selected and sorted according to CD4, CD3, and IFN-γstatus. (**B**) The percentages of $Th17^+$ cells and $Th1^+$ cells in the dorsal skin were detected by flow cytometry. The data are expressed as average values ± SD, n=5, n represent the number of mice in each group. **P*<0.05, ***P*<0.01, *** *P*<0.001, **** *P*<0.0001.

lesions compared with a patient's native psoriasis plaques showed significant up-regulation of IL-10 and down-regulation of IL-17A and IL-12p40.[31] Moreover, imiquimod-mediated inflammation is strongly dependent on the presence of γδT cells, while pathogenic T cells in psoriasis patient plaque have been shown to be αβT cells.[32] Despite this, the imiquimod mouse model is one of the most heavily utilized acute mouse models for studying psoriasis pathogenesis and evaluating potential therapies.[33]

Cladribine (2-CdA) is a purine nucleoside analogue that preferentially accumulates in lymphocytes, which are rich in deoxycytidine kinase- an enzyme essential for phosphorylating 2-CdA to its active cytotoxic metabolite.[34] Cladribine exhibits cytotoxic effects on both dividing and nondividing lymphocytes by inducing DNA strand breaks, cell death, and apoptosis.[35] Cladribine has been demonstrated to inhibit cytokine secretion by T cells.[36] Laugel et al reported decreases in the production of IL-2, IL-10, IFN-γand TNF-αin T cells treated with

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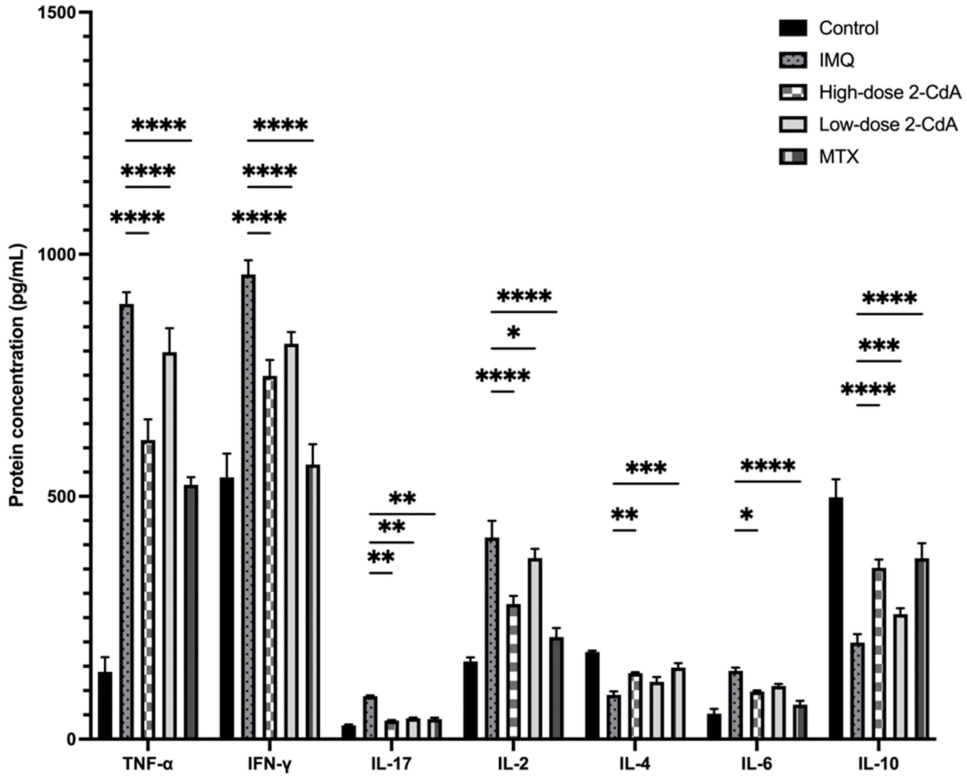

Figure 4 Effect of 2-CdA on the serum cytokine profile. The concentrations of TNF-α, IFN-γ, IL-17, IL-2, IL-4, IL-6, and IL-10 in the serum were measured using ELISA. The data are expressed as average values ± SD, n=5, n represent the number of mice in each group. **P*<0.05, ***P*<0.01, *** *P*<0.001, **** *P*<0.0001.

cladribine in *vitro*.[37] The application of cladribine in patients with severe psoriasis is considered an alternative treatment approach compared to other immunomodulatory regimens, as supported by anecdotal reports in the literature.[17]

This study is the first effort for systematic assessment of the effects of cladribine on a murine model of psoriasis. Our findings confirmed that cladribine could ameliorate the symptoms and pathological features of IMQ-induced psoriasis in mice. The hyperproliferation of epidermal cells in the skin was mitigated, correlating with the downregulated expression of PCNA. Furthermore, cladribine exerted systemic effects in IMQ-treated mice, significantly reducing the frequency of Th17 and Th1 cells within the psoriatic skin. The serum levels of the Th1 cytokines (TNF-α, IFN-γ, and IL-2) and Th17 cytokine (IL-17) were also dramatically reduced by cladribine. These results suggested that cladribine suppressed both the Th17- and Th1-associated cytokines, as well as the psoriatic skin changes induced by IMQ.

When evaluating the efficacy of high-dose cladribine versus low-dose cladribine in a murine model of psoriasis, we observed a dose-dependent therapeutic response. High-dose cladribine resulted in reduced $PCNA^{+}$ cells in epidermis and lower percentages of Th17 and Th1 cells compared with the low-dose group. Furthermore, we addressed the question whether cladribine exerts long-term efficacy on IMQ-induced psoriasis. High-dose cladribine had a sustained inhibition effect on IMQ-induced psoriasis. Consistent with previous studies, cladribine has been shown to possess long-term immuno-modulatory effects on the immune cells.[36] Therefore, cladribine might alter the long-term course of psoriasis through an aggressive initial treatment approach, potentially facilitating long-lasting PASI100 responses.

In conclusion, our study suggested a possible therapeutic role for cladribine in the treatment of IMQ-induced psoriasis in mice. Further investigation is necessary to elucidate how cladribine's mechanism of action shapes the inflammatory milieu in the setting of imiquimod-induced psoriasis, and more importantly, in naturally occurring human psoriasis. Additionally, given that 2-CDA is a cytotoxic substance, its application should be considered

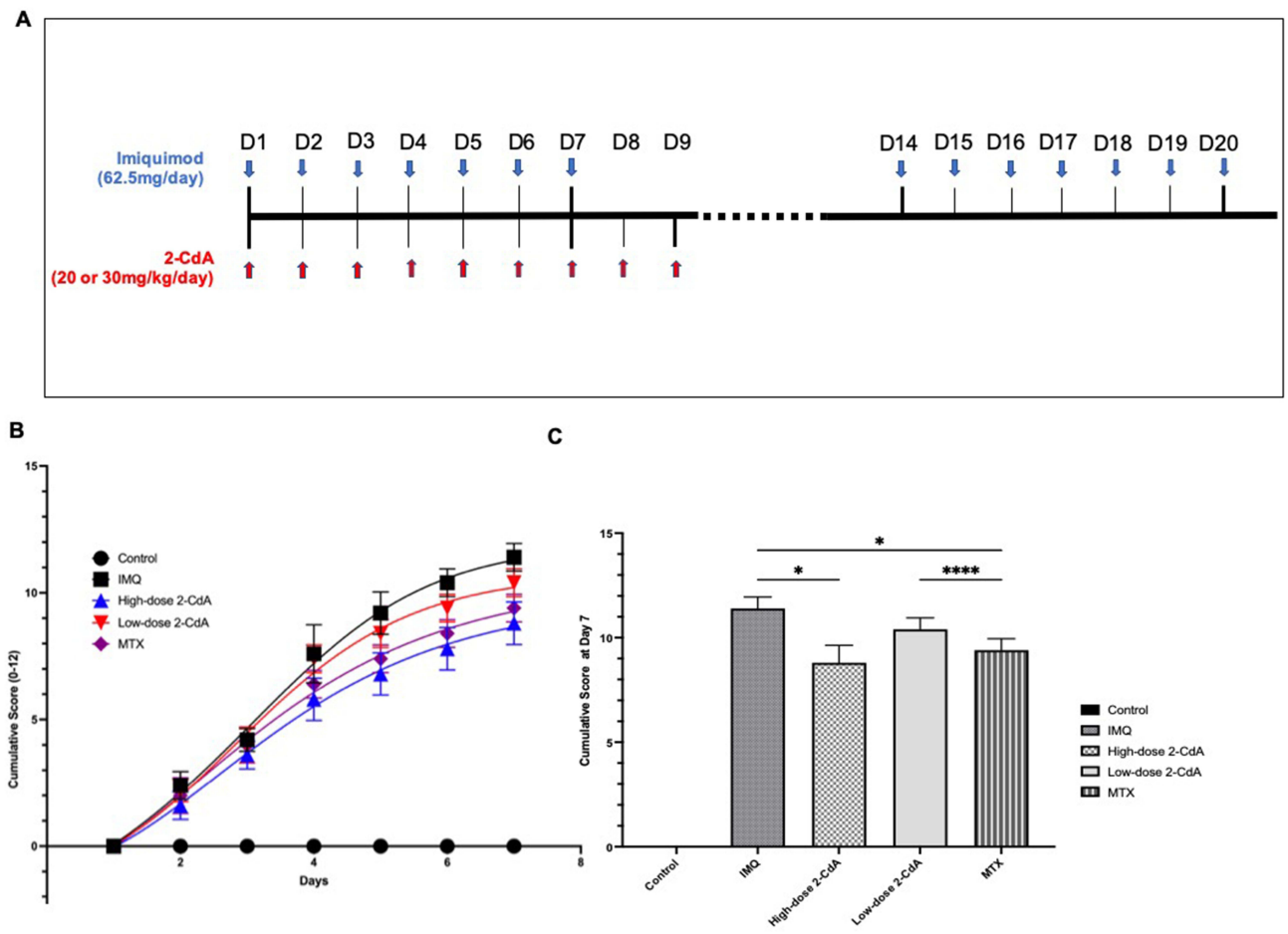

Figure 5 The long-term efficacy of 2-CdA on IMQ-induced psoriasis. (**A**) After five drug half-lives of 2-CdA (5 days), we performed second round of topical IMQ application for 7 days. (**B**) Time-course of cumulative score. (**C**) The cumulative scores on day 7 were statistically assessed. The data are expressed as average values ± SD, n=5, n represent the number of mice in each group. **P*<0.05, **** *P*<0.0001.

only after careful analysis on benefits and safety, particularly when other treatment options have been exhausted. Future clinical trials should be conducted to further validate the effectiveness of cladribine in the treatment of psoriasis.

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Disclosure

There is no conflict of interest within the manuscript.

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