Risk of skin atrophy induced by short-term topical corticosteroid use in atopic dermatitis lesional skin: A systematic review

To the Editor: Concerns related to topical corticosteroid (TCS)-associated skin atrophy limit treatment adherence in patients with atopic dermatitis (AD).[1] We aimed to systematically review the literature on TCS use in patients with AD and individuals with unaffected skin to determine whether AD-related skin changes protect against TCS-associated skin atrophy.

This PROSPERO-registered (CRD42023389887) systematic review was conducted according to the PRISMA guidelines.[2] MEDLINE and Embase were searched for variations of the terms "corticosteroid" and "skin atrophy" from database inception on November 11, 2022 (Supplementary Table I, available via Mendeley at https://data.mendeley.com/datasets/rrjtbz3rym/1). Prospective studies on TCS monotherapy in patients with AD or unaffected skin clinically assessed as skin atrophy were included. Two authors independently screened/assessed the studies, and discrepancies among them were resolved by discussion. The Naranjo analysis was used to evaluate the likelihood of association between TCS and skin atrophy.[3]

Overall, 39 studies (32 AD and 7 non-AD studies) on 6580 patients with AD and 205 unaffected skin application sites were included (Fig 1). Only children were included in 50% of AD studies, only adults were included in 22% studies, and both were included in 28% studies (Table I). Non-AD studies included only adults. Moderately potent TCS was the most common type in AD (41%) and non-AD (35%) studies, and the median duration of treatment was 3.8 (range: 1-240) and 6.1 (0.7-8) weeks, respectively. The most common regimen for both groups was twice-daily application. None of the patients with AD and 21% of unaffected TCS application sites used occlusive application. Thirteen (0.2%) of 6580 patients with AD and 66 (32%) of 205 unaffected application sites developed atrophic changes. TCS was the probable cause of AD- and non-AD-related skin atrophy in 85% and 94% of cases, respectively (Supplementary Table II, available via Mendeley at https://data.mendeley.com/datasets/rrjtbz3rym/1).

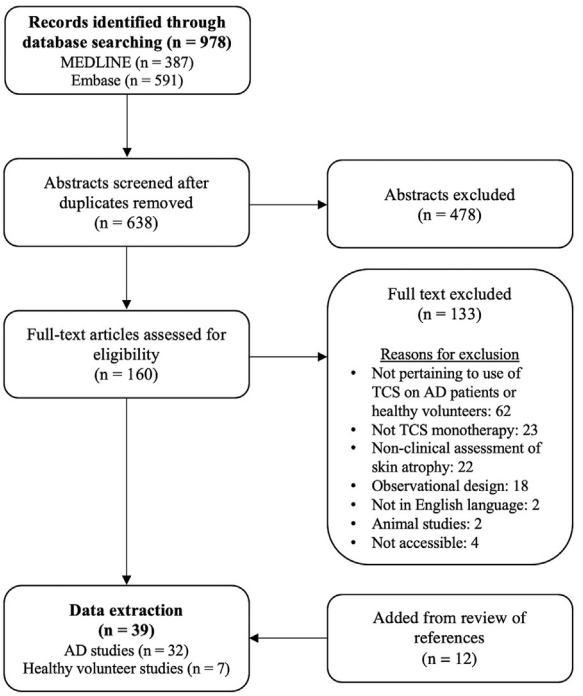

Fig 1. Flowchart diagram for the selection of studies.

Limitations include the small number of non-AD studies and imbalanced TCS exposure between groups.

Our study showed infrequent TCS-associated skin atrophy in AD trials, with approximately one-third of smooth skin TCS application sites developing atrophic changes. Making comparisons between AD and non-AD studies is challenging because non-AD studies exposed individuals to longer periods, higher TCS potency, and occlusive application. Nonetheless, our findings are consistent with an umbrella review (38 systematic reviews/meta-analyses) showing no significantly increased risk of skin atrophy with 2- to 4-week TCS treatment vs emollient/vehicle use (2 randomized clinical trials [RCTs]: (1) 0 of 196 children with skin atrophy with ultra-high-potency TCS vs 0 of 33 children with skin atrophy with vehicle and (2) 6 of 109 children with skin atrophy with high-potency TCS vs 2 of 50 children with skin atrophy with vehicle; $P = .69$).[1] Assessments of once- vs twice-daily application (1 RCT, $n = 94$), intermittent application vs vehicle (5 RCTs, $n = 993$), and occlusive treatment (2 observational studies, $n = 44$) revealed no cases of skin atrophy.[1] A longer-term (1-year) RCT including 330 adults with moderate/severe AD showed a similar trend; low/moderate-potency TCS

Table I. Study and patient characteristics, corticosteroid usage, and cases of skin atrophy reported

Characteristic	Data	
	AD studies (n = 32)	Non-AD studies (n = 7)
Type of study		
Randomized clinical trial, *N* (%)	28 (88)	5 (71)
Prospective controlled study, *N* (%)	2 (6)	0
Prospective uncontrolled study, *N* (%)	2 (6)	2 (29)
Age group		
Children only, *N* (%)	16 (50)	0
Children and adults, *N* (%)	9 (28)	0
Adults only, *N* (%)	7 (22)	7 (100)
Severity of AD		N/A
Moderate to severe, *N* (%)	22 (69)	N/A
Mild to moderate, *N* (%)	5 (16)	N/A
All severities, *N* (%)	3 (9)	N/A
Not reported, *N* (%)	2 (6)	N/A
No. of patients with AD/No. of unaffected TCS application sites	6580	205
Type of TCS used[†]		
Ultra-high-potency, *N* (%)	3 (9)	53 (26)*
High-potency, *N* (%)	10 (31)	50 (24)*
Medium-potency, *N* (%)	13 (41)	72 (35)*
Low-potency, *N* (%)	6 (19)	30 (15)*
Duration of treatment (wk) median [range]	3.75 [1-240]	6.1 [5 d-8 wk]*
Regimen		
Twice-daily application, *N* (%)	24 (75)	106 (52)*
Once-daily application, *N* (%)	3 (9.4)	55 (27)*
Twice-daily and once-daily application, *N* (%)	2 (6.3)	0*
Once-daily and 3 times daily application, *N* (%)	1 (3.1)	0*
Twice-weekly, *N* (%)	1 (3.1)	0*
Three times weekly, *N* (%)	0	44 (21)*
Not reported, *N* (%)	1 (3.1)	0*
Application under occlusion, *N* (%)	0	44 (21)*
No. of patients with AD or No. of unaffected TCS application sites with signs of skin atrophy, *N* (%)	13 (0.2)	66 (32)*

AD, Atopic dermatitis; *N/A*, not applicable; *TCS*, topical corticosteroid.
[†]When multiple TCS were used, the highest-potency one was recorded.
*The data are presented based on the number of application sites due to non-AD studies reporting the body location-specific application of different TCSs.

use on 83.4% of study days, with continued use by 50% of patients, resulted in 3 (0.9%) of 330 cases of skin atrophy.[4]

Chronic AD skin changes may contribute to the low rate of TCS-induced skin atrophy. AD-related hyperplasia/hyperkeratosis can increase the stratum corneum thickness by 100%,[5] potentially requiring higher TCS exposure to achieve clinically significant atrophic changes compared with unaffected skin.

Recognizing the rarity of TCS-induced skin atrophy in patients with AD and educating patients/caregivers on application practices targeting AD lesional skin and avoiding smooth skin is essential to improve treatment adherence and disease outcomes. In the future, measuring skin thickness may aid in validating this hypothesis in AD RCTs assessing TCS therapy.

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Conflicts of Interest

Drs Ricardo, Gosch, Wang, Mr Wright, and Dr Jorizzo have no conflicts of interest relevant to the content of the submission.

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