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COMMENTARY

Re-Evaluating Limitations in Atopic Dermatitis Meta-Analysis Is Important in Interpreting its Results

Limitations of Atopic Dermatitis meta-analysis

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ABSTRACT

A recently published systematic review and meta-analysis concludes that topical calcineurin inhibitors (TCIs) used in atopic dermatitis (AD) increase risk of lymphoma. We believe this study has weaknesses that have not been adequately addressed by the authors and its results must therefore be interpreted with caution. According to study results only pimecrolimus used for AD was statistically significantly associated with lymphoma, and not TCIs in general. Unclear participant baseline immunocompetence and short follow-up duration limit the study's ability to detect malignancy risk. AD has been linked to an increased risk of lymphoma; however, cutaneous lymphoma can be misdiagnosed as AD, which makes it possible that the disease itself rather than treatment with TCIs could account for any increased likelihood of lymphoma in these patients. It is important that clinicians not be wrongfully made more reserved and insecure about prescribing TCIs in the future.

Keywords: Atopic dermatitis; Topical calcineurin inhibitors; Tacrolimus; Pimecrolimus; Lymphoma

Key Summary Points

A recently published systematic review and meta-analysis concluded that topical calcineurin inhibitors (TCIs) used in atopic dermatitis (AD) increase risk of lymphoma

Due to methodological weaknesses, such as unknown immunocompetency status of AD patients upon inclusion and relatively short follow-up time, as well as difficulty in the differential diagnosis of AD and cutaneous lymphoma, the results of this study may have not been reached safely

Safety of TCIs had already been proved

It is important to not wrongfully make clinicians more reserved and insecure about prescribing TCIs in the future

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COMMENTARY

Lam et al.'s [1] systematic review and meta-analysis concludes that topical calcineurin inhibitors (TCIs) used in atopic dermatitis (AD) increase risk of lymphoma. The results of this meta-analysis should be interpreted with caution due to limitations already presented by the authors in the "Limitations" section of the paper. We believe additional limitations exist.

According to presented results, the approximately twofold increase of lymphoma risk after tacrolimus use was not statistically significant (risk ratio 2.20, 95% CI – 0.96 to 5.07). Therefore, only pimecrolimus use for AD is potentially associated with lymphoma (risk ratio 1.82, 95% CI – 1.27 to 2.60).

The authors have excluded conference abstracts and unpublished studies from their search, thus leading to publication bias [2]. "Gray literature" should have been identified by expanding the search to conference-abstract compendia, books, theses, study registries, etc., and by contacting known researchers in the field.

Included studies have weaknesses. First, participant status of immunocompetence at study commencement is unknown, e.g., previous treatment with systemic immunosuppressants or topical corticosteroids. Additionally, participants were recruited with the first prescription of a TCI. It is therefore unclear to what extent, if at all, TCIs contributed to future malignancies. Second, most included studies had a short follow-up duration time (approximately 4 years), which limits their ability to detect malignancy risk.

Hui et al., Margolis et al. and Schneeweiss et al. [1] (TCI and lymphoma studies) sourced their patients from national US registries; there is therefore a chance that at least some patients were included in more than one study. Hui et al. used "eczema" rather than AD to identify participants in searched databases. Cai et al. documented a link between tacrolimus and B-cell or lymphoid leukemia, with malignancy cases being very few to reliably sustain a statistical association.

Another essential weakness of this study's conclusion is that AD has been linked with an increased risk of lymphoma, which means that the disease itself, rather than its treatment, could account for any increased likelihood of lymphoma in these patients [3]. What is more, cutaneous T cell lymphoma can be misdiagnosed as AD and treated with TCIs (reverse causality bias) [4]. Last, TCIs are minimally absorbed after topical application, which makes them a rather unlikely cause of systemic malignancy [5].

All things considered, the safety of TCIs has already been proved. According to a 2007 US case-control study, which sourced its data from a large health plan database, 249 out of 293,253 patients with AD developed lymphoma (incidence rate 81/100,000 person-years) [6]. Cases were compared with AD patients, who were followed up for a similar amount of time without developing lymphoma, and TCI use was not associated with increased risk of lymphoma: pimecrolimus (odds ratio [OR] 0.80, 95% CI 0.40–1.60), tacrolimus (OR 0.80, 95% CI 0.40–1.70), and topical steroids, pimecrolimus and tacrolimus used concomitantly (OR 1, 95% CI 0.30–4.10) [6].

We believe that identifying all possible limitations is important to avoid increasing the already existing concern about a possible association of TCIs and lymphoma, which could wrongfully make clinicians more reserved and insecure in prescribing TCIs in the future. In any case, when treating AD patients, the benefit of TCI administration should always be weighed against any potential side effects.

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REFERENCES

1. Lam M, Zhu JW, Tadrous M, Drucker AM. Association between Topical Calcineurin Inhibitor Use and Risk of Cancer, including Lymphoma, Keratinocyte Carcinoma, and Melanoma: A Systematic Review and Meta-analysis [Internet]. JAMA Dermatology. American Medical Association; 2021 [cited 2021 Jun 2]. p. 549–58. https://jamanetwork.com/journals/jamadermatology/fullarticle/2778024. Accessed 2 June 2021.

2. Walker E, Hernandez A V., Kattan MW. Meta-analysis: Its strengths and limitations [Internet]. Cleve. Clin. J. Med. Cleveland Clinic Educational Foundation; 2008 [cited 2021 Jun 2]. p. 431–9. https://pubmed.ncbi.nlm.nih.gov/18595551/. Accessed 2 June 2021.

3. Mansfield KE, Schmidt SAJ, Darvalics B, Mulick A, Abuabara K, Wong AYS, et al. Association between Atopic Eczema and Cancer in England and Denmark. JAMA Dermatology [Internet]. American Medical Association; 2020 [cited 2021 Jun 2];156:1086–97. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7315391/. Accessed 2 June 2021.

4. Kelati A, Gallouj S, Tahiri L, Harmouche T, Mernissi FZ. Defining the mimics and clinico-histological diagnosis criteria for mycosis fungoides to minimize misdiagnosis. Int J Women's Dermatology [Internet]. Elsevier Inc; 2017 [cited 2021 Jun 2];3:100–6. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5440453/. Accessed 2 June 2021.

5. Billich A, Aschauer H, Aszódi A, Stuetz A. Percutaneous absorption of drugs used in atopic eczema: Pimecrolimus permeates less through skin than corticosteroids and tacrolimus. Int J Pharm Elsevier. 2004;269:29–35.

6. Arellano FM, Wentworth CE, Arana A, Fernández C, Paul CF. Risk of lymphoma following exposure to calcineurin inhibitors and topical steroids in patients with atopic dermatitis. J Invest Dermatol [Internet]. J Invest Dermatol; 2007 [cited 2021 Oct 16];127:808–16. https://pubmed.ncbi.nlm.nih.gov/17096020/. Accessed 16 Oct 2021