ACTAS Dermo-Sifiliográficas xxx (xxxx) xxx–xxx

ACTAS
Dermo-Sifiliográficas

Full English text available at
www.actasdermo.org

CASE AND RESEARCH LETTER

Addition of Antihistamines to Therapy With Isotretinoin for Moderate to Severe Acne: A Friendly Summary of the Body of Evidence (FRISBEE)

Adición de Antihistamínicos a la Terapia con Isotretinoína para el Acné Moderado a Severo: Resumen Estructurado de Revisiones Sistemáticos (FRISBEE)

To the Editor,

Acne is the most common skin disease, affecting up to 85% of adolescents.[1] Isotretinoin, a derivative of vitamin A, represents the therapy of choice in most cases of moderate-to-severe acne, due to its ability to act on the 4 main pathophysiological factors of acne: follicular hyperkeratinization, sebum hypersecretion, presence of Cutibacterium acnes, and inflammation.[1] Nonetheless, the use of isotretinoin must be monitored due to its potential adverse effects, which include xerosis, cheilitis, headache, myalgia, hepatotoxicity, hypertriglyceridemia, and teratogenicity, among others.[2,3]

In 2008, Pelle et al. conducted an in vitro study, in which they evidenced the presence of histaminergic receptors in sebocytes, as well as a decrease in squalene levels associated with the use of antihistamines.[4] Since then, a potential role for antihistamines in the treatment of acne has been hypothesized, due to their anti-inflammatory and antipruritic action, and their ability to reduce lipogenesis in sebocytes.[1] Similarly, it has been proposed that the addition of antihistamines to isotretinoin therapy may have a synergistic therapeutic role and attenuate its adverse effect profile.[1–3,5]

Therefore, we aimed to assess the safety and efficacy profile of combined therapy with antihistamines and

Table 1 Summary of findings (SoF) table.

Antihistamines + isotretinoin vs isotretinoin monotherapy for moderate-to-severe acne			
Patients	Adolescents and adults with moderate-to-severe acne		
Intervention	Antihistamines[a] + isotretinoin[b]		
Comparison	Monotherapy with isotretinoin[b]		
Outcome	Absolute effects	Relative risk (95%CI)	Certainty of evidence (GRADE)
	Isotretinoin / Antihistamines + isotretinoin		
	Difference: patients per 1000		
Decrease in lesion count by week 12	Combination therapy vs isotretinoin monotherapy resulted in a greater decrease from baseline in non-inflammatory lesion count (44.8% vs 17.8% in 1 study[1]; 63.2% vs 44.5% in another trial[3]); in inflammatory lesion count (55.8% vs 22.9% in 1 study[1]; 75.9% vs 62.7% in another trial[3]); and in total lesion count (45.6% vs 18.7% in 1 study[1]; 66.07% vs 48.7% in another trial[3]), with statistical significance. Another study[5] reported these outcomes as the count difference between both groups, also favorable to the combined therapy.	–	⊕⊕⊕◯[e] Moderate

https://doi.org/10.1016/j.ad.2025.02.028

Please cite this article as: V. Meza, A. Figueroa, D. Saavedra et al., Addition of Antihistamines to Therapy With Isotretinoin for Moderate to Severe Acne: A Friendly Summary of the Body of Evidence (FRISBEE), ACTAS Dermo-Sifiliográficas, https://doi.org/10.1016/j.ad.2025.02.028

Table 1 (*Continued*)

Outcome	Absolute effects		Relative risk (95%CI)	Certainty of evidence (GRADE)
	Isotretinoin	Antihistamines + isotretinoin		
	Difference: patients per 1000			
Decrease in the *Global Acne Grading System* (GAGS) score by week 12[c]	Combination therapy showed a greater decrease in the *GAGS* score with respect to baseline vs monotherapy (63.1% vs 17.2% in 1 study[2]; 51.0 vs 38.5% in another trial[3]), in a statistically significant manner.		–	⊕⊕⊕◯[e] Moderate
Patient satisfaction[d]	One study[1] showed that the mean patient satisfaction score was 3.4 (SD, 0.15) in the intervention group, and 2.75 (SD, 0.18) in the control group (statistically significant difference, $P = 0.008$). Similarly, another trial[3] found that in the intervention group, 42.1% of patients were ''very satisfied'' vs 22.8% from the control group.		–	⊕⊕⊕◯[e] Moderate
Paradoxical exacerbation	298 per 1000	104 per 1000	RR, 0.35 (0.16–0.75)	⊕⊕⊕◯[e] Moderate
	Difference: <194 (Margin of error: from <250 to <74)			
Adverse effects	All studies reported the presence of adverse effects. One study[1] found a lower rate of cheilitis (75% vs 90%) and pruritus (15 vs 45%) in the intervention group vs the control group. A lower rate of pruritus was also described by 2 other studies favorable to the intervention group (12.9% vs 71% in one trial[2]; and 18% vs 50% in the other[3]). No severe adverse events were reported.		–	⊕⊕◯◯[f] Low

[a] 2 studies used desloratadine at a dose of 5 mg/d, while another 2 studies used levocetirizine in doses of 5 mg/d.
[b] Isotreninoin doses were 20 mg/d (approximately, 0.2–0.4 mg/kg/d).
[c] The *GAGS* divides the face, chest and back into 6 areas (forehead, each cheek, nose, chin and chest/back), and assigns a factor to each area based on the surface area and distribution/density of the pilosebaceous units. Each type of lesion is given a value depending on its severity (no lesions = 0, comedones = 1, papules = 2, pustules = 3 and nodules = 4), and the score for each area (local score) is calculated using this formula: local score = factor x rating (0– 4). The overall score is the sum of all local scores. Scores from 1 to 18 are representative of mild acne; 19-30, moderate; 31–38, severe; and > 39, very severe acne[1–5].
[d] The *4 point-scale* was used, in which patients categorize their degree of satisfaction as: 4, very satisfied; 3, satisfied; 2, slightly satisfied; 1, unsatisfied.
[e] 1 level of evidence was downgraded due to risk of bias.
[f] 2 levels of evidence were downgraded due to risk of bias and imprecision.

isotretinoin vs the use of isotretinoin as monotherapy, for moderate-to-severe acne.

We conducted an electronic search in Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. Data from the primary studies were extracted from the systematic reviews and, then, reanalyzed. Subsequently, a meta-analysis and a *Summary of Findings* (SoF) table using the *Grading of Recommendations, Assessment, Development and Evaluation* (GRADE) approach were conducted.

We identified a total of 3 systematic reviews[6–8] including 5 primary studies overall,[1–3,5,9] 4 of which were randomized trials (262 patients).[1–3,5] Our analysis was based on the 4 randomized trials and is shown in Table 1.

In conclusion, the addition of antihistamines to isotretinoin therapy vs the use of isotretinoin as monotherapy likely decreases the counts of non-inflammatory lesions, inflammatory lesions and total lesions by week 12 (moderate certainty of evidence). On the other hand, the combination therapy likely decreases the *Global Acne Grading System* score by week 12; probably decreases the risk of paradoxical exacerbations; and likely increases patient satisfaction vs monotherapy with isotretinoin (moderate certainty of evidence). Finally, combined therapy may reduce the adverse effects derived from isotretinoin therapy, in particular cheilitis and pruritus (low certainty of evidence).

Informed consent

Not applicable.

Data access statement

The authors declare their full availability for the delivery of data upon request.

Funding

None declared.

Conflicts of interest

None declared.

Acknowledgments

None declared.

References

1. Lee HE, Chang IK, Lee Y, Kim CD, Seo YJ, Lee JH, et al. Effect of antihistamine as an adjuvant treatment of isotretinoin in acne: a randomized, controlled comparative study. J Eur Acad Dermatol Venereol. 2014;28:1654–60.
2. Van TN, Thi LD, Trong HN, Van TC, Minh TT, Minh PPT, et al. Efficacy of oral isotretinoin in combination with desloratadine in the treatment of common vulgaris acne in vietnamese patients. Open Access Maced J Med Sci. 2019;7:217–20.
3. Pandey D, Agrawal S. Efficacy of isotretinoin and antihistamine versus isotretinoin alone in the treatment of moderate to severe acne: a randomised control trial. Kathmandu Univ Med J (KUMJ). 2019;17:14–9.
4. Pelle E, McCarthy J, Seltmann H, Huang X, Mammone T, Zouboulis CC, et al. Identification of histamine receptors and reduction of squalene levels by an antihistamine in sebocytes. J Invest Dermatol. 2008;128:1280–5.
5. Van TTD, Thuong NV, Trang TTH, Ha VT, Luyen VTH, Tung VT, et al. Efficacy of oral isotretinoin in combination with levocetirizine in management of severe acne vulgaris. Dermatology. 2019;29:60–8.
6. Fahrurodzi DS, Thadanipon K, Rattanasiri S, Thakkinstian A. Antihistamine as an adjunctive treatment in acne vulgaris: a systematic review and meta-analysis. Asian J Soc Hum. 2023;2:1504–21.
7. Hsieh CY, Tsai TF. Use of H-1 antihistamine in dermatology: more than itch and urticaria control: a systematic review. Dermatol Ther. 2021;11:719–32.
8. Wang L. Antihistamine: a useful medication with minimal adverse drug reactions to improve acne symptoms and reduce sebum production. Sch Phys Assist Stud. 2015:508.
9. Yosef A, Dawoud NM, Gharib K. Preliminary evaluation of the clinical efficacy of antihistamines as an adjuvant treatment to isotretinoin for acne vulgaris. J Egypt Women's Dermatol Soc. 2017;14:49–55.

V. Meza[a,*], A. Figueroa[a,b], D. Saavedra[a,b], F. Valenzuela[a,c]

[a] *Department of Dermatology, Universidad de los Andes, Santiago, Chile*
[b] *Department of Dermatology, Clínica Dávila, Santiago, Chile*
[c] *Department of Dermatology, Universidad de Chile, Santiago, Chile*

* Corresponding author.
E-mail address: victormezaviteri@gmail.com (V. Meza).