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CONSENSUS DOCUMENT

[Translated article] Iberia Consensus on Strategies to Prevent and Manage Irritation by Topical Retinoids in Facial and Trunk Acne



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KEYWORDS

Facial and trunk acne; Consensus; Topical retinoids; Irritation

Abstract

Objective: To assess the level of agreement on various prevention and management strategies for irritation caused by topical retinoids in facial and trunk acne in an attempt to alleviate it and minimize treatment discontinuations as much as possible.

Method: After reviewing the scientific medical literatura currently available, 4 different areas of uncertainty in the management of irritation caused by topical retinoids in acne were identified. A questionnaire with 34 recommendations was created and evaluated by a group of 133 dermatologists (Delphi methodology).

Results: In 82.3% of the recommendations (28 out of 34), some level of agreement was reached (\geq 85% agreement in 22 recommendations and \geq 70% agreement in 6). The results with the highest level of agreement focused on specific patient education strategies (explaining that irritation is an expected reaction at the beginning of treatment and tends to decrease over time), gradual and/or spaced application of topical retinoids (at night time to prevent and/or reduce skin irritation), and the importance of using adjuvant products, specific for acne-prone skin, hydration, photoprotection, and skin cleansing. These recommendations reflect a comprehensive approach to managing irritation associated with topical retinoids and promoting long-term adherence.

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Conclusions: Skin irritation caused by topical retinoids in facial and trunk acne is an expected, mild, and controllable reaction if proper prevention and management guidelines are followed, meaning that it should not be a reason for treatment discontinuation.

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Consenso Iberia sobre estrategias de prevención y manejo de la irritación por retinoides tópicos en acné localizado en cara y tronco

Resumen

Objetivo: Conocer el grado de acuerdo en diversas estrategias de prevención y manejo de la irritación por retinoides tópicos en acné facial y troncal con la finalidad de mejorarla y evitar, en la medida de lo posible, abandonos de tratamientos.

Método: Tras revisar la literatura, se identificaron 4 áreas de incertidumbre en el manejo de la irritación por retinoides tópicos en acné. Se desarrolló un cuestionario con 34 recomendaciones que fueron evaluadas por un grupo de 133 dermatólogos (metodología Delphi).

Resultados: En un 82,3% de las recomendaciones (28 de 34) alcanzó algún grado de acuerdo (22 consenso con \ge 85% de acuerdo y 6 mayoría con \ge 70% de acuerdo). Los resultados con mayor grado de acuerdo se centraron en estrategias específicas de educación del paciente (explicar que la irritación es una reacción esperable al inicio del tratamiento y que tiende a disminuir con el tiempo), aplicación gradual y/o espaciada de los retinoides tópicos (por la noche para prevenir y/o reducir la irritación de la piel) y la importancia de usar productos adyuvantes, específicos para piel con acné, para la hidratación, fotoprotección y limpieza de la piel. Estas recomendaciones reflejan un enfoque integral para gestionar la irritación asociada a retinoides tópicos y fomentar su adherencia a largo plazo.

Conclusiones: La irritación de la piel por retinoides tópicos, en acné facial y troncal, es una reacción esperable, leve y controlable si se siguen unas correctas pautas de prevención y manejo, y no debería ser motivo de abandono del tratamiento.

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Introduction

PALABRAS CLAVE

Retinoides tópicos;

Consenso;

Irritación

Acné facial y troncal;

Acne is a highly prevalent chronic inflammatory disease worldwide, affecting approximately 80% of adolescents (from 13 to 18 years old)¹ that usually grows into adulthood. In its most severe or persistent forms, it leads to a series of psychosocial effects that can negatively impact the patient's quality of life.²

Currently, retinoids (both oral and topical) are the gold standard to treat acne as first-line therapy according to the main national and international clinical practice guidelines. $^{3-6}$

The first topical retinoid for acne therapy was tretinoin, also known as retinoic acid, which was approved by the U.S. Food and Drug Administration (FDA) in the 1970s.⁷ Since then, other retinoids such as isotretinoin, adapalene, and trifarotene have also been approved and are currently marketed in Spain and Portugal to treat acne.⁸

Retinoids work by activating nuclear retinoic acid receptors in the skin. These receptors regulate gene expression, which in turn can improve cell turnover, reduce sebum production, and increase collagen production.⁹ However, this process can also cause skin irritation. Retinoids can increase the production of enzymes that degrade collagen and skin proteins, leading to dryness, peeling, and redness. Additionally, retinoids can alter the skin lipid barrier, making it more susceptible to water loss and, therefore, drier, more sensitive, and more prone to irritation.^{10,11}

Although skin irritation is considered a sign that treatment is working,¹² as it indicates that the skin is experiencing faster cell turnover, excessive irritation can be counterproductive and cause the patient to abandon the treatment.¹³

In our routine dermatological clinical practice, we are used to managing the tolerability issues associated with retinoids, using different strategies to minimize potential irritation. These include: 1) training the patient on the correct application of treatment, especially within the first few weeks, and 2) using cosmetics as adjuncts to maintain proper hygiene and hydration of the affected area.

However, literature supporting these strategies is scarce, as well as information on how to properly prevent or efficiently treat tolerability issues associated with topical retinoids in facial and truncal acne. This knowledge and these skills should become part of the expertise of all health professionals involved in the management of acne.

The objective of this consensus document was to validate a series of recommendations aimed at improving the approach to patients with acne and the tolerability of topical retinoid therapies. We consider these recommendations of great interest to health professionals often dealing with acne patients, including dermatologists, general practitioners, and pediatricians.

Method

Selection of participants

One scientific committee for the project was established, including 8 dermatologists (7 Spanish and 1 Portuguese) focused on facial and truncal acne. The committee, with methodological assistance, defined the objectives, scope, and sections of the document. Four major topic groups were addressed: 1) preferences for topical acne treatment; 2) skin irritation and topical acne treatment with retinoids; 3) recommendations/guidelines to prevent/reduce skin irritation in topical acne treatment with retinoids; and 4) extreme weather conditions and skin irritation and topical acne treatment with retinoids acne treatment with retinoids.

Literature review and preliminary recommendations

A literature review (PUBMED and COCHRANE) on recommendations and strategies to improve the tolerability of topical retinoids in acne treatment was conducted. With the information obtained, the scientific committee created a series of preliminary recommendations.

Scientific committee meetings

The scientific committee met twice to review and confirm the objectives, scope, and sections of the document. Subsequently, the results of the literature review and the provisional recommendations were presented and discussed. This led to the definition of 34 final recommendations.

Delphi

The 34 final recommendations were subjected to consensus using the Delphi method¹⁴ to establish the level of agreement on such recommendations.

This was done online through Google Forms and, in addition to the scientific committee, these recommendations were submitted to 125 dermatologists (108 Spanish and 17 Portuguese). Votes were cast on a Likert scale¹⁵ from 1 (totally agree) to 5 (totally disagree). Consensus was defined when, at least, 85% of participants voted ≤ 2 (totally agree and agree), and majority when, at least, 70% of participants voted ≤ 2 . Recommendations with a level of agreement < 85% in the 1st round of voting were voted in a 2nd Delphi round (the cutoff values did not change from the 1st to the 2nd Delphi round). This methodology was selected due to its common and recent use in the field of acne.^{16,17}

Results

Consensus was reached on 22 recommendations (64.70%), 19 in the 1st round and 3 in the 2nd round. A total of 6 recommendations (17.65%) achieved a majority consensus, as opposed to another 6 (17.65%) which did not (fig. 1). The

34 RECOMMENDATIONS

- > 22 consensus (> 85% level of agreement reached)
- 6 majority consensus (> 70% to < 85% level of agreement reached)
- 6 no consensus/majority consensus (< 70% level of agreement reached)

Figure 1 Overall consensus based on the level of agreement.

results of the 2 rounds of voting on the 34 recommendations are presented in table 1.

Block A. On the preferences for topical acne therapy

When prescribing a topical treatment for facial and truncal acne, what experts value most is its efficacy and tolerability, with a 95.5% and 90.2% level of agreement respectively reached in the 1^{st} round. Simplicity in the routine/dosage achieved a 75.9% level of agreement in the 1^{st} round and majority consensus in the 2^{nd} round with a 82.7% level of agreement.

Recommendation #4. Skin irritation is a barrier to prescribing a topical treatment.

Since only 64.7% of participants agreed with this statement in the 2nd round, it did not reach consensus. That skin irritation is a barrier to prescribing a topical treatment is a debatable and nuanced issue, as experts consider it a limiting factor only if appropriate measures to prevent or treat irritation are not taken, such as prescribing specific non-comedogenic moisturizers or spacing out applications if necessary. With proper precautions, skin irritation should not be an obstacle to prescribing topical retinoids for facial or truncal acne.

Recommendation #5. The waiting time to obtain results is a barrier to prescribing a topical treatment.

This statement received a < 50% (47.10%) level of agreement in the 2nd round, and was, therefore, unable to reach consensus. The lack of agreement on this issue created some controversy within the group, as-a priori-the waiting time to see the first results was considered a relevant variable since patients usually prefer quick results. Any retinoid (whether oral or topical) takes time before the first results are noticeable, being a common thing for oral retinoids to cause an initial worsening of acne within the first weeks of treatment.¹⁸ One expert recommended starting with topical—before oral—retinoid treatment to avoid the usual initial worsening associated with oral retinoids.

There are patients for whom topical retinoid treatment would be indicated regardless of the time it takes to achieve results, such as patients who do not meet criteria for oral treatment, patients who need combined therapies (oral and topical), and those requiring maintenance with topical retinoids after finishing oral retinoid treatment.

Recommendation #6. Photosensitivity is a barrier to prescribing a topical treatment.

With only 30.10% agreement in the 2nd round, this statement received the lowest level of agreement of all consensus

No. Recommendation 1 ⁴⁴ round % agreement 2 rd round % agreement 2 rd round % disagreement Final result BLOCK A - ON PREFERENCES FOR TOPICAL ACMET TREATMENT messibility a topical treatment is its EFFICACY 95.0% - CONSENSUS 2 What I value most when prescribing a topical treatment is its TOLERABILITY 90.0% - CONSENSUS 3 What I value most when prescribing a topical treatment is its SIMPLICITY in the ROUTHE/DOSAGE 75.0% 82.70% MAJORITY 4 Skin IRRITION is a barrier to prescribing a topical treatment to treatment ADD TOPICAL ACME TREATMENT to prescribing a topical treatment to treatment ADD TOPICAL ACKE TREATMENT WITH RETINOIDS NO CONSENSUS 8LOCK A - ON SINI IRRITATION AND TOPICAL ACKE TREATMENT WITH RETINOIDS CONSENSUS CONSENSUS 1 Skin irritation tends to DECREASE gradually over time suddenside effect 98.0% - CONSENSUS 1 Skin irritation tends to DECREASE gradually over time submit that temperature is to prescribing a topical treatment tends to have fewer skin irritation tends to DECREASE gradually over time submit that temperature is to PREVENT AdVICA CREDUCE by following proper guidelines/rcommendations/ tentistis how PROVENT 94.70% - CONSENSUS <td< th=""><th>Table 1 De</th><th>elphi results.</th><th></th><th></th><th></th><th></th></td<>	Table 1 De	elphi results.					
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	14	WASHING THE FACE with specific products in the morning to remove retinoid residues helps PREVENT and/or	79.70%	87.97%		CONSENSUS	

Table 1 (Co	ontinued)				
No.	Recommendation	1 st round % agreement	2 nd round % agreement	2 nd round % disagreement	Final result
15	DRYING THE FACE ''BY PATTING'' (without rubbing) helps PREVENT and/or REDUCE skin irritation	77.40%	89.47%		CONSENSUS
16	SPACING OUT topical retinoid applications helps PREVENT and/or REDUCE skin irritation	99.20%	*		CONSENSUS
17	Combining treatment with specific non-comedogenic moisturizers with SPF helps PREVENT and/or REDUCE skin irritation	94.00%	*		CONSENSUS
18	The wash-off technique (applying treatment, waiting 30-60 minutes, and washing the face with a specific product) helps PREVENT and/or REDUCE skin irritation	60.90%	75.94%		MAJORITY
19	I find the following standard administration protocol for starting topical retinoid treatment for acne to be correct - SEE FIGURE 3	88.00%	*		CONSENSUS
	EXTREME WEATHER CONDITIONS A			NE TREATMENT WIT	
20	It is preferable to START topical retinoid treatment for acne when the WEATHER IS NOT EXTREME	63.20%	67.67%		NO CONSENSUS
21	The time of year DOES NOT MATTER when starting topical retinoid treatment for acne	39.80%	39.85%		NO CONSENSUS
22	I prefer to INTERRUPT topical retinoid treatment during periods of EXTREME WEATHER in ANY patient	14.30%		88.72%	CONSENSUS
23	IN PATIENTS WHO HAVE BEEN ON THERAPY FOR A SHORT PERIOD OF TIME, I prefer to DISCONTINUE topical retinoid treatment during periods of EXTREME WEATHER	15.80%	6.80%	81.95%	MAJORITY
24	In PATIENTS WHOSE ACNE IS ALREADY UNDER CONTROL, I suggest spacing out treatment when it coincides with periods of EXTREME WEATHER	57.90%	78.20%		MAJORITY
25	If the PATIENT TOLERATES topical retinoids WELL and HAS NO IRRITATION, it is NOT necessary to DISCONTINUE treatment at any time of year	92.50%	*		CONSENSUS
26	During extreme weather conditions, I prefer my patients to SPACE OUT the applications of topical retinoids	43.60%	59.40%		NO CONSENSUS

Table 1	(Continued)				
No.	Recommendation	1 st round % agreement	2 nd round % agreement	2 nd round % disagreement	Final result
27	By following good application guidelines and recommendations, I consider that it is NOT NECESSARY to DISCONTINUE topical retinoid treatment during periods of extreme weather (intense cold or high sun exposure)	88.70%	*		CONSENSUS
28	With good sun protection (SPF 30-50), topical retinoids can be prescribed at ANY time of year	87.20%	*		CONSENSUS
29	Good sun protection (SPF 30-50) helps PREVENT and/or REDUCE SUN EXPOSURE IRRITATION in skin treated with topical retinoids	92.50%	*		CONSENSUS
30	Good MOISTURIZATION WITH SPF with specific non-comedogenic products helps PREVENT and/or REDUCE irritation during periods of intense cold	97.00%	*		CONSENSUS
31	PROTECTING THE SKIN WITH APPROPRIATE CLOTHING (long sleeves, hats, etc.) during periods of EXTREME WEATHER helps PREVENT and/or REDUCE irritation in skin treated with topical retinoids	86.50%	*		CONSENSUS
32	I avoid topical retinoid treatment in patients with FAIR SKIN TYPES during periods of high sun exposure	25.60%	12.80%	81.20%	MAJORITY
33	Irritation due to photosensitization from topical retinoids is a VERY COMMON issue in my clinical practice	21.10%	9.02%	80.50%	MAJORITY
34	It is important to REAPPLY sun protection if spending a long time outside, sweating excessively, or if the patient showers/bathes	94.70%	*		CONSENSUS

Criteria for consensus on each recommendation were established if 85% or more of the group members indicated their agreement with the statement in either one of the 2 rounds and the criteria for majority consensus if 70% or more of the participants indicated their agreement with the recommendation in either one of the 2 rounds of voting.

* Recommendations with > 85% majority consensus in the 1st round were not submitted for voting in the 2nd round.

statements. It is well-known that sun exposure should be avoided while on topical retinoids,⁷ which is why it was particularly notable that there was no agreement on this issue. After analyzing the results, the expert committee explained this lack of agreement by considering that photosensitivity is not a barrier *per se* since there are easily accessible and applicable tools (photoprotectors) for patients. None

Table 1

(Continued)

of the experts, from the Iberian Peninsula or the Balearic and Canary Islands, would refrain from prescribing a topical treatment due to photosensitivity. Even in some cases with a high risk of photosensitivity, topical retinoid treatment might be preferred over full-dose oral retinoids, which can have more side effects of irritation and photosensitivity than a properly applied topical treatment.

Block B. On skin irritation and topical acne treatment with retinoids

The 6 recommendations voted in this block reached consensus (level of agreement \geq 85%) in the 1st round, making it the block with the highest level of agreement among all those evaluated.

Recommendation #8. Mild and controllable skin irritation frequently occurs at the beginning of treatment.

Recommendation #10. It is important to tell the patient that temporary irritation is normal and expected and, therefore, treatment should not be discontinued.

These 2 recommendations achieved consensus with a 98.5% level of agreement. Consensus was unanimous regarding irritation being associated with topical retinoid treatment as an expected, mild, and controllable side effect at the beginning of treatment that tends to decrease over time. The entire expert committee agreed on the importance of explaining how retinoids work to avoid treatment discontinuation due to a lack of results within the first few days of treatment or poor tolerability.

Recommendation #7. I consider that irritation is an expected reaction at the start of treatment and not an undesirable side effect.

Recommendation #12. Patients who follow the application recommendations/guidelines properly tend to have fewer skin irritation problems than those who do not.

These 2 issues reached consensus with a 94.7% level of agreement in the 1st round. The experts showed a high level of agreement on the importance of explaining patients that if they apply the guidelines/recommendations properly, they will have fewer tolerability issues, and that they should not discontinue treatment despite initial irritation since it is not an undesirable side effect (except for very sensitive skin).

Recommendation #11. Skin irritation can be prevented and/or reduced by following correct application guide-lines/recommendations.

A total of 97% of participants considered that skin irritation treated with topical retinoids can be prevented/reduced if the proper guidelines/recommendations are followed. The expert committee summarized the main recommendations in Figure 2.

Block C. On recommendations/guidelines to prevent/reduce skin irritation in topical acne treatment with retinoids

In this block, a total of 7 recommendations were evaluated, 4 of which reached consensus in the 1st round. Specifically, *recommendation #16*, ''spacing the applications of topical retinoids helps prevent and/or reduce skin irritation,'' with a 99.2% level of agreement, was the recommendation that obtained the highest level of agreement among all the issues on which votes were cast.

Recommendation #13. Applying topical retinoid correctly at night helps prevent and/or reduce skin irritation.

Recommendation #17. Combining treatment with specific non-comedogenic moisturizers and SPF helps prevent and/or reduce skin irritation.

These 2 recommendations achieved broad consensus, with 91% and 94% levels of agreement, respectively in the 1^{st} round as strategies to improve the tolerability of topical retinoid treatment.

Recommendation #14. Washing the face with specific products in the morning to remove retinoid residues helps prevent and/or reduce skin irritation.

Recommendation #15. Drying the skin by patting (without rubbing) helps prevent and/or reduce skin irritation.

These 2 recommendations reached consensus in the 2nd round with a nearly 90% level of agreement in both cases (see detailed results in table 1). The expert committee considers these 2 measures of paramount importance regarding good tolerability associated with topical retinoids: washing the face in the morning to remove the residues of the treatment applied the night before with specific non-comedogenic products and doing so carefully without rubbing the skin when drying.

Recommendation #18. The wash-off technique (applying treatment, waiting 30 to 60 minutes, and washing the face with a specific product) is a measure that helps prevent and/or reduce skin irritation.

In the 2nd round, "the wash-off technique (applying treatment, waiting 30 to 60 minutes, and washing the face with a specific product) is a measure that helps prevent and/or reduce skin irritation" that obtained a majority level of agreement with 76%. Although this technique can slow down the process of applying treatment, it is an interesting technique for very sensitive skins, especially within the first few days of treatment.

Recommendation #19. I find the following standard administration protocol for initiating topical retinoid treatment for acne to be correct (see figure 2).

A total of 88% of voters found the standard administration protocol for initiating topical retinoid treatment for acne presented in Figure 3 to be correct in the 1st round. Having a validated schedule to start a topical retinoid treatment was a requirement that the expert committee considered necessary when sharing these recommendations with other medical professionals.

Block D. On extreme weather conditions and skin irritation and topical acne treatment with retinoids

With 15 recommendations, this block was the most extensive of the 4 and generally obtained the lowest level of agreement: 8 issues reached consensus (7 in the 1^{st} round and 1 in the 2^{nd} round), 4 issues achieved a majority consensus, and 3 did not reach any levels of agreement.

Recommendation #20. It is preferable to START a topical retinoid treatment for acne when the weather is not extreme.

Recommendation #21. The time of year does not matter when starting a topical retinoid treatment for acne.

Neither of these 2 issues, with 67.7% and 39.8% levels of agreement, respectively, in the 2nd round, reached consensus or a majority consensus either.

Starting topical retinoid treatment during extreme weather conditions, i.e., periods of high sun exposure (summer months in the Iberian Peninsula) or intense cold (winter months in the Iberian Peninsula), were the issues that gen-



Figure 2 Recommendations from the expert group to prevent/reduce skin irritation in the topical treatment of acne with retinoids.



Figure 3 Standard administration protocol for starting topical retinoid treatment for acne. $\sqrt{}$ indicates the nights when the topical retinoid should be applied.

erated the most controversy within this block. The expert group concluded that, considering that the use of topical retinoids in extreme weather conditions is closely related to irritation (cold) and photosensitization (heat/sun), it seems logical that these issues did not reach consensus (which is consistent with recommendations #4 and #6 from block A, which also did not reach consensus).

Recommendation #26. During extreme weather conditions, I prefer my patients to space out the applications of topical retinoids.

This recommendation received a 59.4% level of agreement in the 2^{nd} round, not reaching a majority consensus or consensus for that matter. The expert committee clarified that the need to space out applications does not depend so much on the time of year but on the tolerability and the phase of the treatment the patient is in. Spacing out applications is a recommended and widely used measure at the beginning of the treatment or when the patient experiences a high level of irritation, regardless of the weather.

Recommendation #32. I avoid topical retinoid treatment in patients with fair skin types during periods of high sun exposure.

A majority disagreement was reached (81.2% in the 2nd round) that, in patients with fair skin phototypes, it is not necessary to avoid topical retinoid treatment during periods of high sun exposure. In fact, although it can occur in any patient, post-inflammatory hyperpigmentation in acne patients is more common in darker skin types.¹⁹ The expert committee emphasized that in any patient, the proper application of photoprotection provides protection regardless of the patient's skin type.

Recommendation #33. Irritation due to photosensitization by topical retinoids is a very common issue in my clinical practice.

There was a majority disagreement (80.50% in the 2nd round of voting) that irritation due to photosensitization induced by topical retinoids is a very common issue in the dermatologists' office. Some experts acknowledged not having seen any patients with photosensitization due to top-ical retinoids, but some with photosensitization due to oral retinoids.

Discussion

This document presents a series of strategies and practical recommendations on how to reduce or prevent tolerability issues of topical retinoids to treat facial and truncal acne. The Delphi methodology was followed and followed by a large group of dermatologists from Spain and Portugal, thereby reinforcing the validity of the recommendations.

Notably, a high level of agreement was reached on the recommendations (fig. 1): 82.3% of them, 28 out of 34, achieved some level of agreement (22 reached consensus with a \geq 85% level of agreement and 6 reached a majority consensus with a \geq 70% level of agreement).

Consensus was almost unanimous (94.7%) that patients who properly follow the application recommendations/guidelines (fig. 2) tend to have fewer tolerability issues than those who do not. These recommendations are simple and very easy to apply, so it is essential to disseminate them widely both to the medical community and to patients.

Based on the consensus results and its own experience, the expert committee concluded that topical retinoidrelated skin irritation is an expected, mild, and controllable reaction if correct prevention and management guidelines are followed. Therefore, it should not be a reason to discontinue treatment, which is why the expert committee emphasized the importance of dedicating part of the consultation to explaining the various strategies to the patient and recommended providing supporting materials for the patient.

With this consensus, the expert committee fulfills the objective of this project: to provide recommendations endorsed by a large panel of dermatologists, helping other health care professionals treating acne improve topical retinoid treatments for facial and truncal acne.

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