Formulation and Usage Regime Approaches to Improve Retinol Tolerance

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Abstract

Whilst retinol is well-known to have beneficial effects on the appearance of photoaged skin, high concentrations are often associated with consumer tolerance issues. We therefore aimed to compare the tolerance profiles of two high concentrations of retinol, 0.3% and 1%. In a second study, we assessed whether formulation design and regime changes could improve the tolerance profile.

We first recruited 218 female participants with age-related facial skin concerns to study one; a 6 week at-home tolerance study where one cohort tested a 0.3% (w/w) retinol formulation and a second cohort tested an identical 1% (w/w) retinol formulation, following a specified usage regime. We followed this up with a second 8-week consumer tolerance study on 208 female participants. This time applying a re-formulated 1% (w/w) retinol formulation, followed by the application of a post-retinol soother product, ramping up retinol usage more slowly. Participants self-reported any reactions they had with 'tolerant and mild' being the main measure of acceptability.

In study one, in the 0.3% retinol cohort 88.7% of participants were classed as 'tolerant or mild' compared to 62.1% in the 1% cohort. In study two, in the cohort testing a re-formulated 1% retinol product with a post retinol soother product, 73.5% were classed as 'tolerant or mild'.

This suggests 0.3% is better tolerated than 1% retinol. However, a formulation re-design with soothers and barrier-supporting ingredients, combined with the use of a post retinol soothing product and a slower ramp up regime, was able to improve the tolerance profile of 1% retinol.

Key words: Retinol, tolerance, formulation design, regime, photoageing

Introduction

Retinol is well-known to have beneficial effects on the appearance of photoaged skin, with numerous studies showing the ability of retinol to improve parameters including the appearance of lines and wrinkles, mottled pigmentation and measures of elasticity and firmness [1, 2, 3, 4, 5]. However, retinol is often associated with consumer tolerance issues due to retinol-associated irritancy [6], especially at higher concentrations [3].

Despite this, there is a still a demand for high concentration retinol products due to their greater potency, and concentrations as high as 1% can be found on the cosmetic market. There is a need therefore to understand more about the tolerance profiles of high strength retinol products and identify approaches to mitigate the potential for irritation as much as possible.

In this study we aimed to compare the tolerance profiles of two high strength concentrations of retinol, a 0.3% (w/w) formulation and a 1% (w/w) formulation. In a second study, we then further assessed whether formulation design, regime guidance and the addition of a specialised supporting product to the regime could improve the tolerance profile of the highest concentration; 1% retinol.

Materials and Methods

We recruited 218 female participants (aged 35 – 70 years old) with facial age-related skin concerns including lines and wrinkles and uneven skin tone/pigmentation to study one; a 6 week at-home tolerance study where one cohort (n=115) tested a 0.3% (w/w) retinol formulation and a second cohort (n=103) tested an identical 1% (w/w) retinol formulation. Both oil-in water (o/w) emulsion products contained retinol in an oil and inulin encapsulation system. Formulations were applied at night-time only, ramping up usage over the study period to eventual nightly use after 4 weeks (table 1). Participants were instructed to follow retinol application with their own night-time moisturiser, using this moisturiser even on evenings when retinol was not applied. All participants applied an SPF day cream each morning of the study.

Table 1: Application regimen in 6-week tolerance study

Week	Application Frequency	Application Number
1	Twice a week on non-consecutive evenings	Application 1+2
2	Twice a week on non-consecutive evenings	Application 3+4
3	Three times a week on non-consecutive evenings	Application 5-7
4	Three times a week on non-consecutive evenings	Application 8-10
5	Every evening	Application 11-17
6	Every evening	Application 18-24

We followed this up with a second study; an 8-week consumer tolerance study on 208 female participants (aged 35-70) with facial age-related skin concerns, including deep lines and wrinkles and uneven skin tone/pigmentation. This time applying a re-formulated 1% (w/w) retinol formulation; containing the same encapsulated retinol but with additional soothing and barrier supporting ingredients including bisabolol and niacinamide, followed by the application of a specially designed post-retinol soother product containing further barrier-supporting and soothing ingredients. These ingredients included bisabolol, niacinamide, a blend of ceramides and an extract from the plant Ophiopogon japonicus. In this study participants ramped up usage of retinol more slowly over the study period, reaching nightly use on average after 6 weeks, but only as the skin could tolerate (table 2). The post retinol soother product was applied nightly throughout the study, even on evenings when retinol was not applied. All participants applied an SPF day cream each morning of the study.

Table 2: Application regimen of the retinol formulation in the 8-week tolerance study. The below were upper limits, with guidance to use as frequently as the skin could tolerate.

Week	Application Frequency	Application Number (max.)
1	Twice a week on non-consecutive evenings	Application 1+2
2	Twice a week on non-consecutive evenings	Application 3+4
3	Twice a week on non-consecutive evenings	Application 5+6
4	Twice a week on non-consecutive evenings	Application 7+8
5	Three times a week on non-consecutive evenings	Application 9-11
6	Three times a week on non-consecutive evenings	Application 12-14
7	Every evening	Application 15-21
8	Every evening	Application 22- 28

In both studies, participants self-reported whether they had any reactions to the retinol formulation and the severity of any reactions they had on a weekly basis, using a classification guide developed by a Dermatologist (Table 3). Participants were grouped according to the most severe reaction reported during the study. A participant, for example, reporting three mild and one moderate reaction would be classified as having had a moderate reaction. Participants not reporting reactions were deemed fully tolerant to the retinol formulation.

No reaction and mild reactions were deemed expected and tolerable based on participant feedback and expert Dermatologist and Toxicologist opinion. Therefore, the primary outcome measure was the percentage of participants in the reaction classification of 'tolerant and mild' as opposed to moderate or severe.

Table 3: The guidelines provided to volunteers to classify their as mild, moderate or severe.

Skin Reaction Classification Key	
1 - MILD	Tingling, stinging, tightness, blemishes/spots, peeling, dryness without soreness, slight redness, slight feeling of heat/burning.
2 - MODERATE	Red, angry and sore to the touch, blind pimples beneath the surface of the skin, large area of dryness, rash.
3 - SEVERE	Red, angry and sore without touching, eczema-like and persistent. Reactions can include broken skin, blistering, extended rash.

Results

In study one, in the 0.3% retinol cohort (n=115), 80 participants (69.6%) reported having no reaction and 22 (19.1%) reported having mild reactions, meaning 88.7% of participants were classed as 'tolerant and mild'. In contrast, In the 1% retinol cohort (n=103), 41 participants (39.8%) reported having no reaction and 23 (22.3%) reported having a mild reaction, meaning 62.1% of participants were classed as 'tolerant and mild' (figure 1). In the 0.3% retinol cohort only 11 participants (9.5%) reported moderate or severe reactions, compared with 39 (37.9%) in the 1% cohort. In the 0.3% cohort 2 participants (1.7%) had reactions which were 'unclassified' as no severity information was received.

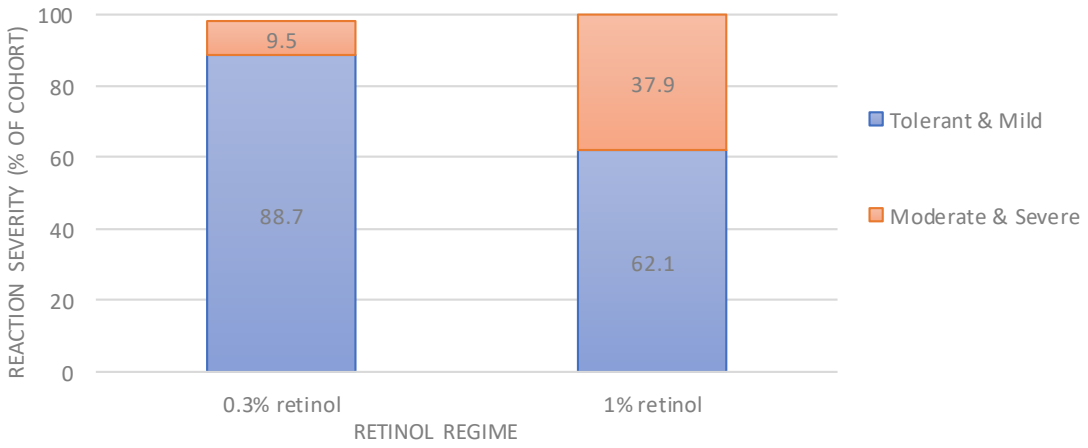

Figure 1: Tolerance profiles of 0.3% compared to 1% retinol, when tested on a cohort of women over a 6-week period following a specified usage regime. Results based on self-reported reaction severity.

In study two, in the cohort testing a re-formulated 1% retinol product with a post retinol soother product (n=208), 77 participants (37%) reported having no reaction and 76 (36.5%) reported mild reactions, meaning 73.5% were classed as 'tolerant and mild' (figure 2). In this study 55 participants (26.5%) reported moderate or severe reactions.

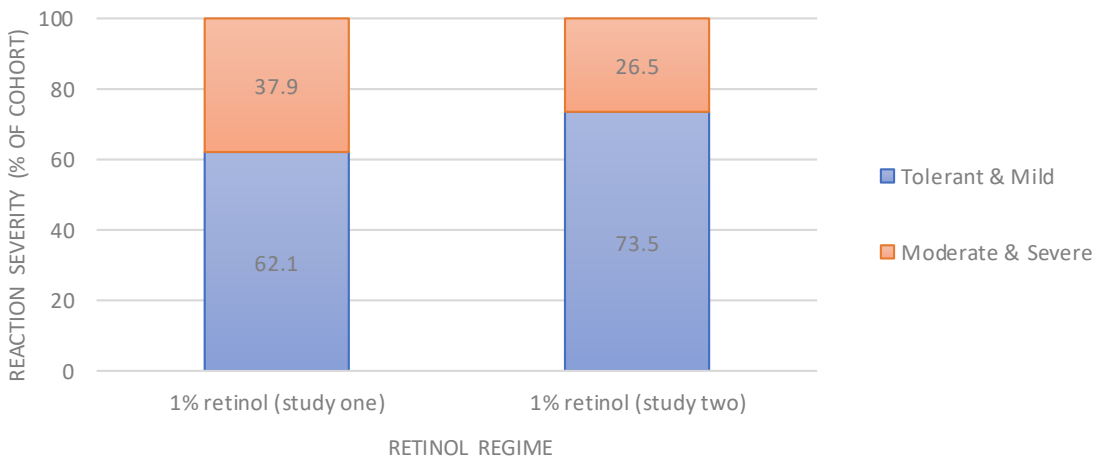

Figure 2: Tolerance profiles of two different 1% retinol formulations and regimes. In study two retinol was re-formulated with additional soothers and barrier-supporting ingredients, combined with a post-retinol soother product and usage was ramped up more slowly over a longer study period (8-weeks vs 6-weeks). Results based on self-reported reaction severity.

Discussion

High strength retinol and all-trans retinoic acid, the dermatologist gold standard treatment for photoaged skin, are associated with skin sensitivity issues which can impact on longer term usage and the overall benefits achieved [7]. These issues such as stinging, redness, peeling and dryness and even soreness are consistent with a disruption of the skin barrier that leads to an increase in skin inflammation, via cytokine production [6].

In this research, we first compared the tolerance profile of a 0.3% retinol o/w facial formulation with that of an identical formulation containing 1% retinol and not surprisingly found that more participants in the 0.3% retinol cohort reported no reactions or mild reactions compared with participants in the 1% retinol cohort. This suggests 0.3% is better tolerated than 1% retinol, a finding in-keeping with a previous study by Gold et al [3] where a 0.5% retinol formulation was found to be better tolerated than a 1% retinol formulation when tested over an 8-week study period, albeit with more modest results over the time period of the study. Interestingly however, a longer-term, 48-week, study on all-trans retinoic acid found that a lower, more tolerable concentration of 0.025% all-trans retinoic acid offered similar benefits clinically to photoaged skin than a higher concentration of 1% [7], suggesting differences in efficacy may be temporal.

Given the consumer demand for concentrations as high as 1% retinol due to their increased potency and potentially faster results, we adopted a number of strategies to try and improve upon this tolerance profile for 1%. Firstly, the 1% retinol formulation was re-designed with the inclusion of ingredients that could both help support a stronger skin barrier and soothe the skin; secondly, the retinol product was combined in a nightly usage regime with a cosmetic soothing and moisturising barrier enhancer; thirdly, usage ramp up was slowed over the 8-week period. The combination of these approaches improved the tolerance profile of 1% retinol with a reduction in moderate and severe reactions observed.

This research provides insights into the impact of retinol concentration on tolerance, as well as formulation and regime approaches for improving consumer tolerance to high concentrations of retinol. Helping inform the responsible development of high strength retinol products for the cosmetic skincare market.

Conclusion

This study suggests that retinol concentration has arguably the biggest impact on consumer tolerance to retinol, but that a combination of formulation design, the speed of ramp up and supporting products can improve the tolerance of high strength retinol. However, even with these approaches there will be a proportion of consumers who will be unable to tolerate 1% retinol, indicating that those new to retinol should start with lower concentrations.

Conflict of Interest

All authors are employees of the No7 Beauty Company.

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