



Research Article

The Retinsphere and BIOPEP 15 Technology, Alone or in Combination with Salicylic and Glycolic Acid in Acne Treatment: A Narrative Review of Current Evidences

Linda Pongetti¹, Flavio Fiorito¹, Alberto Sticchi¹, Antonio Alma¹,
Francesca Farnetani¹, Massimo Milani^{2*}, Marco Manfredini¹

¹Clinical Dermatology University Modena, Italy

²Medical Department, Cantabria Labs Difa Cooper Medical Department, Caronno P

*Corresponding author: Massimo Milani, Cantabria Labs Difa Cooper Medical Department, Caronno P, Italy

Citation: Pongetti L, Fiorito F, Sticchi A, Alma A, Farnetani F, et al. (2023) The Retinsphere and BIOPEP 15 Technology, Alone or in Combination with Salicylic and Glycolic Acid in Acne Treatment: A Narrative Review of Current Evidences. Clin Exp Dermatol Ther 8: 202. DOI:10.29011/2575-8268.100202

Received Date: 13 February 2023; **Accepted Date:** 21 February 2023; **Published Date:** 27 February 2023

Abstract

The combination of retinoids and antibacterial agents are considered as first line treatment approach in subjects with mild to moderate acne. Hydroxypinacolone Retinoate (HPR) is a cosmetic grade ester of all-trans retinoic acid, which is able to bind directly with retinoid receptors without the need for metabolic breakdown to more biologically active forms. It has been demonstrated to possess anti-acne and anti-ageing effects, causing less skin irritation than retinoic acid. The Retinsphere technology, which is a patented dual combination of hydroxypinacolone retinoate in glycosphere-encapsulated retinol, and BIOPEP-15, a plant-derived antimicrobial peptide, is available and used in several anti-acne products. The aim of this narrative review was to summarize all available scientific evidence on topical Retinsphere HPR-BIOPEP-15 (RB) therapy for acne, alone or in combination with nicotinamide, salicylic and glycolic acids (RB+NSG). In detail, 3 studies analysed RB and 2 studies analysed RB+NSG efficacy and tolerability. All studies measured acne lesions count changes over time, two studies analysed microscopic skin changes with Reflectance Confocal Microscopy (RCM), and two studies assessed sebum production changes. In conclusion, collective data derived from current literature demonstrated that RB induced a median 51% reduction of total acne lesion (TL), comprising a 43% reduction of non-Inflammatory Lesions (NIL) and a 67% reduction of Inflammatory Lesions (IL). RB+NSG showed increased efficacy, with an average of 69% reduction of TL, 50% reduction of NIL and a 77% reduction of IL. Both RB and RB+NSG can significantly reduce sebum production (-57%), without affecting skin barrier function and being characterized by a good skin tolerability.

Keywords: Acne; Topical retinoid; Clinical trial

Introduction

Hydroxypinacolone retinoate and BIOPEP-15 for topical acne therapy

Acne treatment guidelines recommend topical retinoid and antimicrobial combination therapy as the first line treatment option in comedonal and mild-to-moderate acne, [1,2]. Various combination therapies have been developed, including tretinoin plus topical antibiotics, and BPO plus antibiotics [3]. Retinoids [4] refer to those chemicals that are structurally or functionally similar to retinol, or vitamin A [5], which is an essential biomolecule for embryonic development and adult body homeostasis [6]. Currently, retinoids are widely used in several fields of medicine and ongoing research is still studying their undiscovered potential [7]. The first retinoid molecule, synthesized in 1955, is 13-cis-retinoic acid or isotretinoin [8]. Since then, over two thousand retinoids have been synthesized [9]. They are typically classified into four generations. Hydroxypinacolone Retinoate (HPR) is a cosmetic grade ester of all-trans retinoic acid, which is able to bind directly with retinoid receptors without the need for metabolic breakdown to more biologically active forms [10]. It has been demonstrated to possess anti-acne and anti-ageing effects, causing less skin irritation than retinoic acid [11]. RetinSphere® is a patented glycospheres system, which acts as a penetration enhancer [12] and a retinoid carrier, containing 0.15% of HPR and retinol. They enhance the delivery of retinol increasing penetration and chemical stability [13]. They are supramolecular configurations, organized around a solid inner core, consisting of modified starch which is powerfully hydrophilic and endows the particle with its chemical and physicochemical stability as well as its biocompatibility. A single layer of fatty acids is covalently grafted at the periphery of this central core, providing the particle with a peripheral lipophilic nature, without modifying its internal hydrophilic nature [14]. BIOPEP-15 is a botanical derived complex that contains an oligopeptide of 15 amino acids, found to possess broad spectrum antimicrobial activity against a wide variety of organisms including antibiotic resistant *C. acnes strains* [15]. BIOPEP-15 acts binding to lipoteichoic acid endotoxin on the outer membrane of cell wall of gram-negative bacteria, enabling access to cytoplasmic membrane with consequent cellular damage. In addition, BIOPEP-15 could

antagonize the lipoteichoic-dependent Toll Like Receptor 2 (TLR2) activation exhibiting a peculiar anti-inflammatory action [16,17,18]. The development of topical HPR and BIOPEP-15 combination showed promising results, characterized by a high efficacy against acne pathogenetic mechanisms and a favourable tolerability profile in several types of acne patients, as such as: adult females 19, sensitive skin patients 20, and African ethnicity patients 21. In this review, we aim to discuss current evidences and updates on the use of HPR and BIOPEP-15 in acne.

Methods

A PubMed and a Google Scholar search was performed to identify articles with the following keywords: “hydroxypinacolone” AND “BIOPEP” AND “acne”. Original articles published from 2015 to 2023 on clinical studies were selected, and related citations were evaluated. Review articles and meta-analyses were excluded. A description and analysis of eligible articles and of their results will be presented.

Results

Clinical evaluations

Clinical efficacy of RB technology was assessed by five studies that enrolled globally 207 subjects (Table 1) [19 -26]. All studies measured acne lesions count changes over time, two studies analysed microscopic skin changes with reflectance confocal microscopy (RCM), and two studies assessed sebum production changes. Additional parameters were: Global Acne Grade System (GAGS) score, investigator global assessment (IGA) score, trans-epidermal water loss (TEWL) and VISIA imaging. Treatment duration lasted from a minimum of 4 weeks to a maximum of 16 weeks. Topical application schedule was once to twice daily. Three studies analysed the efficacy of RB gel formulation technology in subjects affected by mild-moderate acne demonstrating an overall median reduction of 51% (49-77%,) total lesion (TL), 43% (14-60%) non-inflammatory acne lesion (NIL) and 67% (60-70%) inflammatory acne lesions count (IL). Two studies evaluated the efficacy of gel or spray formulation of RB+NSG in subjects with moderate (n=57) acne demonstrating a reduction of 57% and 80% of TL after 4 and 8 weeks of treatment respectively. Studies that assessed GAGS score demonstrated a reduction of 60-78% of acne severity after treatment.

Author	Year of publication	Subjects	Treatment Duration (weeks)	Study Outcomes	Main Results
Veraldi et al* 22	2016	100	12	Acne lesions count. Skin tolerability score GAG score	Significant reduction in acne lesions Significant improvement of GAG score Good skin tolerability
Gabriel et al* 23	2020	30	16	Acne lesion count Sebum production IGA score Skin Tolerability score	Significant reduction in acne lesions. Reduction in sebum production
Manfredini et al* 24	2016	20	6	Acne lesion count RCM parameters	Improvement of acne lesions evaluated by confocal microscopy
Villani et al** 25	2020	25	8	Acne Lesions count GAG evolution score RCM Parameters VISIA Imaging Trans Epidermal Water Loss measurements	Significant reduction in acne lesions. Improvement of acne lesions evaluated by confocal microscopy. No modification of TEWL during treatment
Milani et al.** 26	2021	32	4	Acnes Lesions Count Sebum production	Significant reduction in acne lesions Significant reduction in sebum production

*Studies carried out with product containing Retinsphere and BIOPEP 15 (RB); **Studies carried out with product containing Retinsphere, BIOPEP 15, salicylic acid 2% and glycolic acid 15% and niacinamide 4% (RB+NSG). GAG: Global Acne Grade. IGA: Investigator Global Assessment.

Table 1: Clinical Studies carried out with Retinsphere/BIOPEP Technology in acne.

Skin physiology parameters

Two studies analysed the effect of RB on sebum production [23,26]. Sebum production was measured in all studies using Sebumeter® method (Sebumeter 815, Courage+Khazaka GmbH). The study of Gabriel et al. showed that the use of RB alone induced a 57% reduction in sebum production after 4 months of treatment, while RB+NSG reduced sebum output by 30% after 6 weeks of treatment. Trans epidermal Water loss (TEWL) was evaluated in one study [25]. TEWL was measured by means of a Tewameter 300® device (Courage+Khazaka, electronic GmbH) demonstrating that RB+NSG did not impair or negatively affect the skin barrier function in acne subjects.

Reflectance Confocal Microscopy

Noninvasive imaging techniques have recently outlined precise microscopic features of acne elementary lesions and accurate quantifications for disease severity staging and therapeutical efficacy follow-up [27]. Two studies evaluated the changes of acne skin induced by the application of RB assessed by reflectance confocal microscopy (RCM) [24,25]. Manfredini et al. demonstrated that after 2 weeks, the RCM count of papules and pustules and the RCM scores of exocytosis and dermal

inflammation, decreased substantially. After 4 weeks, the RCM number of comedos was significantly reduced. After 6 weeks, the number of regular follicles increased, while the hyperkeratinized infundibula with thickened bright border decreased significantly [24]. In a study conducted in 25 adult women treated with RB+NSG for 8 week a statistically significant improvement in RCM parameters with reduction of inflammation and infundibular hyperkeratinization following treatment [25].

Skin Tolerability and Safety

The skin tolerability profiles of RB and RB+NSG were good in all the studies analyzed. No severe adverse events were recorded. Veraldi et al. [22] described one hundred acne subjects using RB gel, applied once or twice daily for 3 months. In this trial skin tolerability was evaluated assessing erythema desquamation, burning sensation and xerosis with a semi-quantitative scale ranging from 0(none) to 3 (severe.) with a maximum score value of 12. In this study the global skin tolerability score was 1.14 at day 30, 0.42 at day 60 and 0.26 at day 90. Xerosis (very mild/mild) was reported by 24% of subjects after 30 days and by only 7% (very mild) at the end of treatment period. No differences regarding efficacy or skin tolerability were observed depending on the number of daily applications (once vs. twice). Gabriel et al

reported that the tolerability evaluations reported by Asian subjects treated with RB for 4 months were good in 87-100% individuals at different time period [23]. At the end of the study, all patients (100%) rated tolerability on a semiquantitative scale as 'good'. In the same study, mild itching was experienced by 3-13% of patients from days 15 to 120. Mild burning sensation occurred in 7% of patients at day 45 but was absent at days 90 and 120. No oedema was reported by any of the evaluated patients throughout the study period. Villani et al described the tolerability profile of RB+NSG gel applied for 2 months by 25 women affected by acne was rated as "good" or "very good" by all subjects [25].

Discussion

In mild to moderate acne retinoid therapy combined with antibacterial is considered a reference therapeutic approach [28]. Therapeutic efficacy can improve when keratolytic agents, such as salicylic acid are used in association [29]. The use of topical retinoids is often restrained by the development of irritative dermatitis, exfoliation, dryness, peeling, erythema and pruritus. This is known as retinoid dermatitis or "retinoid reaction", and its occurrence could negatively affect patient's compliance and adherence to the therapeutic regimen [30]. This narrative review summarized the efficacy and tolerability profile of RB and RB+NSG combinations with Retinsphere technology. These two formulations have been evaluated in several studies, comprising a total of 207 subjects affected by mild to moderate acne, and all showing a good efficacy in reducing both IL and NIL. HPR and retinol induce a normalization of keratinocytes differentiation, a decrease of sebum production and a reduction of inflammatory signalling. At the same time, BIOPEP-15, which is a polypeptide with marked anti *C.acnes* activity and immunomodulatory effects, interfere with bacterial wall integrity and inhibit TLR-2 activation, a key pathogenetic mechanism of the inflammatory

processes involved in acne pathogenesis [31]. The RB+NSG product contain also niacinamide, salicylic and glycolic acids. Salicylic and glycolic exert exfoliating and keratolytic activities [32], while niacinamide exert a relevant anti-inflammatory action [33]. Therefore, the RB+NSG formulation combine exfoliating and keratolytic activities and anti-oxidizing action and could be considered as an effective strategy in more severe acne respect to RB alone. Regarding the efficacy of RB and RB+NSG, it is important to consider that the studies included in the present review reported a TL count reduction that varied between 48% and 80% in comparison with baseline. In a recent NICE network meta-analysis, evaluating 39 different therapeutic trials [34,35] on mild-to-moderate acne patients, the average TL percentage reduction was reported around 20-40%. Only 3 trials out of 39 showed an acne TL reduction above 70%. This indirect comparison could support the fact that the efficacy level of RB and RB+NSG products is at least in line with most topical treatments recommended for mild to moderate acne subjects.

Conclusion

The RB technology, alone or in combination with NSG has demonstrated to be a valuable therapy for the reduction of acne lesions (up to -80%) and sebum production (-57%) in subjects with mild acne. The comparison of the results obtained with RB+NSG and RB alone seems to be indicated that RB+NSG therapy is characterized by a faster reduction of acne lesions respect to RB therapy, therefore the former may be a better option for more severe forms of acne compared to the latter. The skin barrier, assessed by TEWL, was not negatively affected neither by RB nor by RB+NSG topical application, and both received good tolerability profile evaluations even by subjects with sensitive skin or different ethnicity.

			Baseline	End Of Study	DELTA	%
RB alone (n = 150)	Veraldi et al * 22	TLC	40,0	15,0	-25,0	-62,5
		IL	10,0	3,0	-7,0	-70,0
		NIL	30,0	12,0	-18,0	-60,0
	Gabriel et al * 23	TLC	28,0	13,7	-14,3	-51,1
		IL	12,7	5,0	-7,7	-60,6
		NIL	15,3	8,7	-6,6	-43,1
	Manfredini et al* 24	TLC	23,3	12,1	-11,2	-48,1
		IL	14,9	4,9	-10,0	-67,1
		NIL	8,4	7,2	-1,2	-14,3
RB+NSG (n = 57)	Villani et al** 25	TLC	5,5	1,1	-4,4	-80,0
		IL [§]	4,0	0,3	-3,7	-92,5
		NIL [§]	1,5	0,8	-0,7	-46,7
	Milani et al.** 26	TLC	22,9	9,8	-13,1	-57,4
		IL	8,7	3,2	-5,5	-63,0
		NIL	14,2	6,5	-7,7	-54,0
Total lesion count (TLC), Non inflammatory lesione (NL) Inflammatory lesions (IL) *Studies carried out with product containing Retinsphere and BIOPEP 15 (RB); **Studies carried out with product containing Retinsphere, BIOPEP 15, salicylic acid 2% and glycolic acid 15% and niacinamide 4% (RB+NSG). [§] Estimate from graphs.						

Table 2: Acne lesion (NI-L; IL; TL) count average percentage reduction and type of treatments.

Conflict of Interest Statement

Linda Pongetti, Flavio Fiorito, Alberto Sticchi, Antonio Alma, Francesca Farnetani and Marco Manfredini have not conflict of interest regarding this article. Massimo Milani MD is an employee of Cantabria Labs Difa Cooper.

References

- Zaenglein Andrea L, Pathy AL, Schlosser BJ, Alikhan A, Baldwin HE, et al. (2016) Guidelines of care for the management of acne vulgaris. J Am acad dermatol 74: 945-973.
- Nast A, Dréno B, Bettoli V, Degitz K, Erdmann R, et al. (2012) European evidence-based (S3) guidelines for the treatment of acne. J Eur Acad Dermatol Venereol 26: 1-29.
- Leyden JJ (2003) A review of the use of combination therapies for the treatment of acne vulgaris. J Am Acad Dermatol 49: S200-S210.
- Fisher GJ, Voorhees JJ (1996) Molecular mechanisms of retinoid actions in skin. FASEB J 10: 1002-1013.
- Bates CJ (1995) Vitamin A. Lancet 345: 31-35.
- Bar-El Dadon S, Reifen R (2017) Vitamin A and the epigenome. Crit Rev Food Sci Nutr 57: 2404-2411.
- Chambon P (1994) The retinoid signaling pathway: molecular and genetic analyses. Semin Cell Boil 5: 115-125.
- Wysowski DK, Swann J, Vega A (2002) Use of isotretinoin (Accutane) in the United States: rapid increase from 1992 through 2000. J Am Acad Dermatol 46: 505-509.
- Ross AC (1993) Cellular metabolism and activation of retinoids: roles of cellular retinoid-binding proteins. FASEB J 7: 317-327.
- TEMOVA RŽ, Škufca P, Kristl A, Roškar R (2021) Retinoid stability and degradation kinetics in commercial cosmetic products. J Cosmet Dermatol 20: 2350-2358.
- RUTH N, MAMMONE T (2018) 1310 Anti-aging effects of retinoid hydroxypinacolone retinoate on skin models. Journal of Investigative Dermatology. 138: S223.
- Cameli N, Cameli N, Mariano M, Abril E, Berardesca E (2012) Clinical evaluation of the efficacy of a new retinoic-complex (Retinsphere®) product for the treatment of skin photoaging. Esperienze Dermatologiche 14: 29-34.
- Banu TS, Sandhya KV, Jayaveera KN (2013) Approaches and Current Trends of Transdermal Drug Delivery System-A Review. Research Journal of Pharmaceutical Dosage Forms and Technology. 5: 177-190.
- Millán CG, Vitale M, Dieulangard M (2016) Evaluation of a new cosmetic combination for melasma treatment in Mexican population. J

- Dermatolog Clin Res 4: 1089.
15. Minkiewicz P, Iwaniak A, Darewicz M (2019) BIOPEP-UWM database of bioactive peptides: Current opportunities. *Int J Mol Sci* 20: 5978.
 16. Sah BNP, Vasiljevic T, McKechnie S, Donkor ON (2018) Antioxidative and antibacterial peptides derived from bovine milk proteins. *Crit Rev Food Sci Nutr* 58: 726-740.
 17. Romics JRL, Dolganiuc A, Velayudham A, Kodys K, Mandrekaret P, et al. (2005) Toll-like receptor 2 mediates inflammatory cytokine induction but not sensitization for liver injury by Propionibacterium acnes. *J Leukoc Biol* 78: 1255-1264.
 18. Hessle CC, Andersson B, Wold AE (2005) Gram-positive and Gram-negative bacteria elicit different patterns of pro-inflammatory cytokines in human monocytes. *Cytokine*. 30: 311-318.
 19. Rubio JM et al. Acne en mujer adulta: Evaluacion de Eficacia y seguridad de un nuevo tratamiento topico frente a las lesiones acneiforme e hyperpigmentacion asociads. GEDET congress 2019 Spain.
 20. Milani M. Clinical-Instrumental Assessment Of The Efficacy And Tolerability Of A Cosmetic Treatment Intended For Sensitive And Acne Prone Skin. Study Report. 22:1-9.
 21. Vitale M Avaliação da eficácia e segurança do uso de Biretix Duo no tratamento da acne leve em pacientes com fototipos cutâneos tipo V-VI (classificação de Fitzpatrick). Study Report. 15109.
 22. Veraldi S, Barbareschi M, Alessandrini G, Cardinali C, Gimma A, et al. (2016) Evaluation of a combination of retinol, hydroxyl-pinacolone retinoate (Retinsphere), an antibacterial agent (BIOPEP. 15), salicylic acid and vitamin E in subjects suffering from predominant comedonal acne—An Italian multicenter prospective open study. *Journal of Dermatology and Clinical Research*. 4: 1072.
 23. Gabriel MTG, Oblepias MSM, Vitale M (2020) Safety and Efficacy of Retinsphere® Technology and BIOPEP-15 in the treatment of Acne in Asian Population. *J Clin Cosmet Dermatol* 4.
 24. Manfredini, Marco, et al. Acne Therapy with a Topical Retinoid and Antibacterial Evaluation of Treatment Efficacy using Confocal Laser Microscopy.
 25. Villani A, Annunziata MC, Cinelli E, Donnarumma M, Milani M, et al. (2020) Efficacy and safety of a new topical gel formulation containing retinol encapsulated in glycospheres and hydroxypinacolone retinoate, an antimicrobial peptide, salicylic acid, glycolic acid and niacinamide for the treatment of mild acne: preliminary results of a 2-month prospective study. *G Ital Dermatol e Venereol* 155: 676-679.
 26. Milani M, Gonzales LC, Villalba M (2021) Efficacy of a Retinoid, Keratolytic, Anti-Inflammatory and Antibacterial Gel and spray Formulations in Mild Common Acne. *Journal of Clinical Dermatology & Therapy*. 089: 2.
 27. Alma A, Sticchi A, Chello C, Guida S, Farnetani F, et al. (2022) Dermoscopy, Reflectance Confocal Microscopy and Optical Coherence Tomography Features of Acne: A Systematic Review. *J Clin Med* 11: 1783.
 28. Feneran AN, Kaufman WS, Dabade TS, Feldman SR (2011) Retinoid plus antimicrobial combination treatments for acne. *Clin Cosmet Investig Dermatol* 4: 79-92.
 29. Draelos Z, Lewis J, McHugh L, Pellegrino A, Popescu L (2016) Novel retinoid ester in combination with salicylic acid for the treatment of acne. *J of Cosmet Dermatol* 15: 36-42.
 30. De Lucas R, Moreno-Arias G, Perez-López M, Vera-Casaño Á, Aladrenet S (2015) Adherence to drug treatments and adjuvant barrier repair therapies are key factors for clinical improvement in mild to moderate acne: the ACTUO observational prospective multicenter cohort trial in 643 patients. *BMC Dermatology*. 15: 1-6.
 31. Beylot C, Auffret N, Poli F, Claudel J-P, Leccia M-T, et al. (2014) Propionibacterium acnes: an update on its role in the pathogenesis of acne. *J Eur Acad Dermatol Venereol* 28: 271-278.
 32. Pirard GE, Kligman AM, Stoudemayer T, Lévêque JL (1999) Comparative effects of retinoic acid, glycolic acid and a lipophilic derivative of salicylic acid on photodamaged epidermis. *Dermatology*. 199: 50-53.
 33. Matts PJ, Oblong JE, Bisset DL (2002) A review of the range of effects of niacinamide in human skin. *International Federation of Societies of Cosmetic Chemists Magazine*. 5: 285-289.
 34. Guideline NG198, Nice (2021) Acne vulgaris: management.
 35. XU J, Mavranetzouli I, Kuznetsov L, Murphy MS, Healy E (2021) Management of acne vulgaris: summary of NICE Guidance. *BMJ*. 374.