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Combined use of topical retinol and oral lactoferrin in mild and moderate acne: a multicenter study

Gabriella Fabbrocini



SUMMARY

BACKGROUND. A number of options have been shown to be effective in mild and moderate acne: topical retinoids, antibiotics, benzoyl

peroxide, salicylic acid and azelaic acid. Recently, the association of topical retinol and oral lactoferrin has been proposed for the treatment of mild and moderate acne. **OBJECTIVE.** To evaluate efficacy and safety of the combined use of topic retinol and oral lactoferrin on mild and moderate acne.

MATERIALS AND METHODS. 107 patients with mild to moderate acne were treated with 0,15% retinol cream gel and oral lactoferrin for 8 weeks. During the course

of the study, no other topical or systemic treatment was allowed. Acne severity and treatment efficacy were evaluated by means of the Global Acne Grading System (GAGS) and a questionnaire about quality of life. Tolerability and acceptability of treatment were recorded, too. **RESULTS.** Most of patients had satisfactory therapeutic response with a reduction of GAGS global score of 51%. No patient dropped out the study because of side effects and tolerability was good/very good in 87,8% of our sample.

CONCLUSIONS. The association of topic retinol and oral lactoferrin can be considered a possible option, quite effective and safe, in mild to moderate acne treatment.

Key words: Acne, retinol, lactoferrin.

Background

Acne pathogenesis is the result of the interaction of several factors. The first relevant factor is an androgen induced hypertrophy of the sebaceous glands with a consequent overproduction of sebum; hyperkeratosis of follicular epithelium, which leads to follicular channel occlusion and accumulation of sebum, is the second one ¹⁻⁶. *Propionibacterium acnes* (*P. acnes*), a Gram-positive anaerobic bacterium that mostly resides in the pilosebaceous follicles of the skin and is a member of the normal skin commensal bacterial flora, is the third relevant factor ⁷⁻¹⁰; *P. Acnes* proliferates in the lipid-rich sebaceous follicles and induces upregulation of inflammatory genes and cytokine secretion ¹¹⁻¹³, through toll-like receptors activation ¹⁴⁻²¹; in addition, *P. Acnes* produces a number of extracellular enzymes and metabolites that can directly damage host tissues ²²⁻²³.

One of the well-known enzymes is extracellular triacylglycerol lipase that produces FFAs by hydrolyzing triglycerides in sebum²⁴.

Sebum FFAs, if overproduced, induce very mild inflammation and assist bacterial adherence and colonization in sebaceous follicles ²⁵⁻²⁷.

Each of the mentioned factors is a potential target for therapy. Placebo-controlled RCTs have shown that a number of options, used either alone or in combination, are effective in the mild and moderate acne treatment: topical retinoids, antibiotics, benzoyl peroxide, salicylic acid and azelaic acid.

In particular, among the several available therapeutic options, topical retinoids have been shown very effective²⁸⁻³⁰.

They are able to reduce significantly the iperseborrhea, thanks to an inhibitory effect on proliferation and differentiation of sebocytes. They also successfully compete with androgen hormones and inhibit the hypercornification ³¹⁻³².

Recently, the association of topical retinol and oral lactoferrin has been proposed for the treatment of mild and moderate acne.

Lactoferrin is an 80 kDa glycoprotein, first identi-

fied in breast milk as a protein product of mammary epithelial cells, belonging to the class of iron chelators and recently considered one of the most important member of the AMPs family (antimicrobial peptides); mammalian peptides with antimicrobial activity in the skin ³³.

Lactoferrin has immunomodulatory, anti-inflammatory and antioxidant activity and it can directly contribute to host defense from bacterial and viral infection ³⁴⁻³⁶.

Objective

The aim of this study was to evaluate efficacy and safety of the combined use of topical retinol and oral lactoferrin on mild and moderate acne.

Materials and methods

The study was conducted between November 2009 and February 2010 in eight different Italian Dermatological Centers (Bari, Bologna, Messina, Milano, Napoli, Torino, Verona) and promoted by Donne Dermatologhe Italia (D.D.I). 107 patients (85 female and 22 males; age from 16 to 24 years; mean age 19,2 years) with mild to moderate acne were enrolled in our study.

All patients were treated with 0,15% retinol gel in MonoDermaDosi[®] (evening application) and oral lactoferrin (1 cap. a day) for 8 weeks (DERMORAL AKN[®]). No other topical or systemic treatment was allowed. The final evaluation was done on 101 patients that completed correctly the 8 weeks treatment.

During the first examination (T0), patients underwent a careful dermatologic visit and received punctual information about the study. All patients signed the informed consent containing the description of the study, the aim, methods and possible side effects.

In order to carry out a comparative analysis, 3 digital photographs (front position, right hemi-face, left hemi-face) were collected and gathered in a database. Acne severity and treatment efficacy

were evaluated by means of the *Global Acne Grading System* (GAGS). This is a quantitative scoring system in which the total severity score is derived from summation of six regional subscores. Each is derived by multiplying the factor for each region (factor for forehead and each cheek is 2, chin and nose is 1 and chest and upper back is 3) by the most heavily weighted lesion within each region (1 for \geq one comedone, 2 for \geq one papule, 3 for \geq one pustule and 4 for \geq one nodule).

The regional factors were derived from consideration of surface area, distribution and density of pilosebaceous units. The "*Global Score*" corresponds to the degree of acne. A score ranging from 1 to 18 identifies mild acne, 19 to 30 moderate acne, 31 to 38 severe acne and \geq 39 very severe acne³⁷. All patients enrolled in our study presented a score between 16 and 24.

Safety variables were tolerability and acceptability of treatment through the evaluation of erythema, dryness, itching, burning sensation and gastrointestinal disorders using a 0-3 qualitative score: 0 = no symptom; 1 = mild symptom; 2 = moderate symptom; 3 = severe symptom.

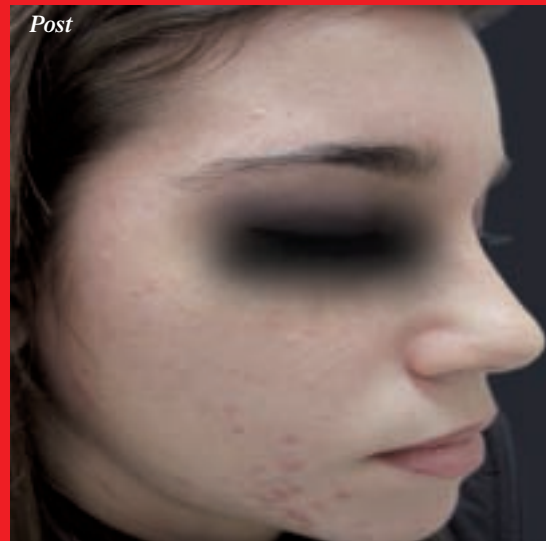
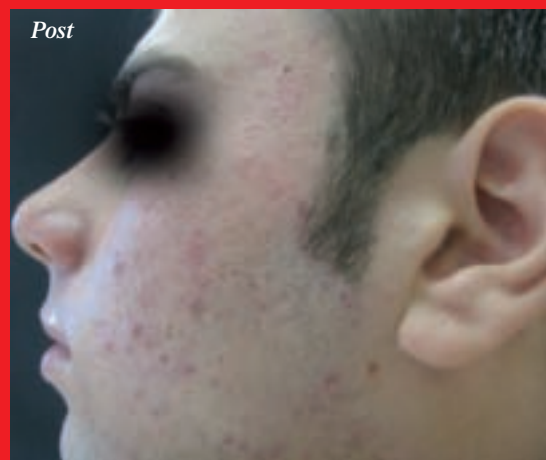
Patients were visited 4 and 8 weeks later (T1 and T2) and, for each of them, 3 digital photos (front position, right hemi-face, left hemi-face) were collected in our database, with the assessment of the GAGS score and safety variables.

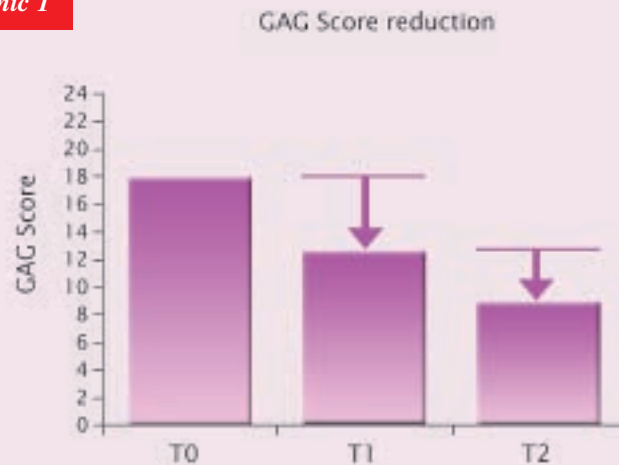
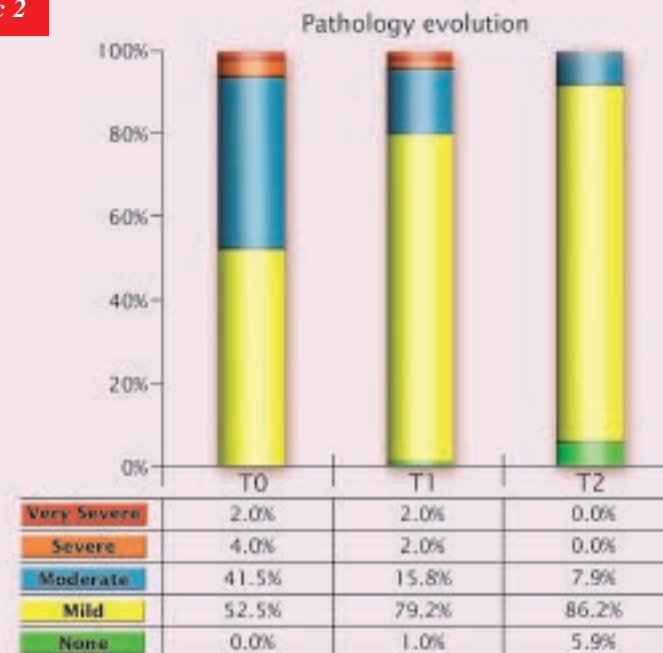
Results

Our study has clearly demonstrated the efficacy and tolerability of the combined use of topical retinol and oral lactoferrin in mild and moderate acne (Figure 1a and b, 2a and b, 3a and b).

All patients treated with topical retinol and oral lactoferrin reported a statistically significant reduction of GAGS global score ($p < 0,01$) 4 and 8 weeks after treatment (T1 and T2) when compared to baseline (T0). It ranged from 16 to 24 at T0, from 10 to 18 at T1 and from 5 to 12 at T3.

The average score was 17.9 at T0, of 12.6 at T1 and 8.9 at T2 with a percentage of GAGS' decreases of 30% after 4 weeks of therapy (T1) and 51% after 8 weeks (T2) (Graphic 1).

*Figure 1a-b.**Figure 2a-b.**Figure 3a-b.*

Graphic 1**Graphic 2**

The positive pathology evolution from (T0) and (T2) is also reported (Graphic 2).

The treatment was safe and well tolerated with a good compliance; patient's opinion as well as doc-

tor's evaluation about treatment's results was satisfactory.

On the whole, patients' compliance and tolerability have been very satisfactory.

In particular, no patient has dropped out the study because of side effects and tolerability has been prevalently good/very good (87,8%); poor/mild tolerability was observed only in 12,2% of patients. Most common adverse reaction have been erythema and irritation; light gastroenteral disorders was observed just in 3 of 101 patients.

Discussion

Our results have shown a clinically relevant and statistically significant decrease of acne lesions using topic retinol and oral lactoferrin. Retinol is able to reduce significantly the iperseborrhea, thanks to an inhibitory effect on proliferation and differentiation of sebocytes; moreover, it successfully compete with androgen hormones and inhibit the hypercornification³¹⁻³².

Oral lactoferrin also has positive effects on acne lesions, due to its biological functions that are been described and critically examined in several studies. Lactoferrin is an 80 kDa multifunctional glycoprotein, first identified in breast milk as a protein product of mammary epithelial cells, belonging to the class of iron chelators³⁴⁻³⁵.

Recent studies have revealed that it can directly contribute to host defense from bacterial and viral infection³⁶.

It is produced by epithelial cells and neutrophil polymorphonuclear leukocytes, and has immunomodulatory, anti-inflammatory and anti-oxidant activity; it regulates iron uptake and cell growth and owns several enzymatic activities³⁸.

The antibacterial activity is due to the ability to destroy or penetrate the bacterial membrane thanks to a peptide called lattoferricin, a fraction of the molecule of lactoferrin, and to the ability of lactoferrin to inhibit bacterial growth by scavenging free iron from fluids and inflamed areas, suppressing free radical-mediated damage³⁹.

Lactoferrin also modulates the immune response with multiple mechanisms that include the production of soluble factors such as cytokines and chemokines, the regulation of production of reactive oxygen species and the recruitment of cells of the immunity defense⁴⁰.

As mentioned below, *P. Acnes* plays a critical role in the development of inflammation in acne when it overgrows and colonizes the pilosebaceous unit. Several *P. Acnes* genes regulate products involved in degrading host molecules and triggering inflammation. In addition, inflammation in acne is also induced by host immune reactions to *P. Acnes*.

P. Acnes produce chemoactive factors that attract the immune system cells such as neutrophils, monocytes, and lymphocytes⁷⁻¹⁰. As reduction in *P. Acnes* numbers in the hair follicle by antimicrobial agents induces clinical improvement, antibiotics are widely prescribed for acne treatment. Unfortunately, long-term antibiotic treatments produce a significant antibiotic resistance, which may cause the antibiotic treatment failure⁴¹⁻⁴³.

Thus, oral administration of lactoferrin might be an alternative option for antibacterial therapy in acne treatment, as its ability to modulate the immune response and elicit strong antimicrobial activity against many bacteria, inhibiting their growth and tissue damage.

Conclusion

Acne pathogenesis is the result of the interaction of several factors. As a consequence, researchers are interested in testing combination therapies in order to reach simultaneously different pathogenetic targets and create more complete treatment strategies. In order to achieve this goal, we evaluated the combined use of topical retinol and oral lactoferrin as an effective and safe therapeutic association for the treatment of mild to moderate acne. It has been widely accepted that lactoferrin exerts antimicrobial action. Thus, oral supplementation of lactoferrin acid may have the potential to be used as an effective antibacterial treatment for antibiotic-refractory acne.

Despite a number of studies on biological effects of lactoferrin have been made, little effort has been conducted to evaluate its potential for acne therapy. Further in-depth research and additional experimentations could be very helpful to confirm and better understand the possible role of oral lactoferrin in mild to moderate acne treatment.

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