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

Gabriella Fabbrocini, Valerio De Vita, Valeria Battimielo, Francesco Pastore, Maria Carmela Annunziata, Maria Chiara Maurello, Annalisa Barba, Cristiano Belloli, Serafina Paola Cannavò, Alessandra Cantù, Anna Luisa Carmagnola, Manuela Carrera, Adriana Ciuffreda, Sandra Farina, Caterina Foti, Valentina Guerrini, Sandra Lorenzi, Paola Nappa, Corinna Rigoni, Maria Carmela Romano
Combined use of topical retinol and oral lactoferrin in mild and moderate acne: a multicenter study

**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. *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. *P. Acnes* proliferates in the lipid-rich sebaceous follicles and induces upregulation of inflammatory genes and cytokine secretion, through toll-like receptors activation; in addition, *P. Acnes* produces a number of extracellular enzymes and metabolites that can directly damage host tissues.

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

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

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 effective.

They are able to reduce significantly the iperseborhea, thanks to an inhibitory effect on proliferation and differentiation of sebocytes. They also successfully compete with androgen hormones and inhibit the hypercornification. 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 mamma-
ry epithelial cells, belonging to the class of iron
chelators and recently considered one of the most
important member of the AMPs family (antimicro-
bial peptides); mammalian peptides with anti-
microbial activity in the skin. Lactoferrin has immunomodulatory, anti-inflam-
matory and antioxidant activity and it can directly
contribute to host defense from bacterial and viral
infection

Objective

The aim of this study was to evaluate effi-
cacy 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 differ-
et Italian Dermatological Centers (Bari, Bologna,
Messina, Milano, Napoli, Torino, Verona) and pro-
moted 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 mod-
erate acne were enrolled in our study.
All patients were treated with 0,15% retinol gel in
MonoDermoDosi® (evening application) and oral
lactoferrin (1 cap. a day) for 8 weeks (DER-
MORAL AKN®). No other topical or systemic
was allowed. The final evaluation was
done on 101 patients that completed correctly the
8 weeks treatment.
During the first examination (T0), patients under-
went 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 possi-
bles side effects.
In order to carry out a comparative analysis, 3 dig-
ital 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 ≥ one comedone, 2 for ≥ one papule,
3 for ≥ one pustule and 4 for ≥ one nodule).
The regional factors were derived from considera-
tion of surface area, distribution and density of
pilosebaceous units. The "Global Score" corre-
sponds 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 ≥ 39 very severe
acne. All patients enrolled in our study present-
ed a score between 16 and 24.
Safety variables were tolerability and acceptability
of treatment through the evaluation of erythema,
dryness, itching, burning sensation and gastroen-
teral disorders using a 0-3 qualitative score: 0 = no
symptom; 1 = mild symptom; 2 = moderate symp-
tom; 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 col-
clected 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 topi-
cal 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).
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 doctor’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 hypercornification 31-32. 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 chelators 34-35. Recent studies have revealed that it can directly contribute to host defense from bacterial and viral infection 36. 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 activities 38. The antibacterial activity is due to the ability to destroy or penetrate the bacterial membrane thanks to a peptide called lactoferricin, 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 damage 39. 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 defense 40.

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 lymphocytes 7-10. 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 failure 41-43. 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.
References


