EFFICACY AND TOLERABILITY OF TOPICAL 0.2% MYRTACINE® AND 4% VITAMIN PP FOR PREVENTION AND TREATMENT OF RETINOID DERMATITIS IN PATIENTS WITH MILD TO MODERATE ACNE

S. VERALDI, G. L. GIOVENE, C. GUERRIERO, V. BETTOLI

VOLUME 147 - No. 5 - OCTOBER 2012
Efficacy and tolerability of topical 0.2% Myrtacine® and 4% vitamin PP for prevention and treatment of retinoid dermatitis in patients with mild to moderate acne

S. Veraldi 1, G. L. Giovene 2, C. Guerriero 3, V. Bettoli 4

Aim. The aim of the present study was to evaluate the efficacy and tolerability of an emulsion of 0.2% Myrtacine® and 4% vitamin PP, compared with a simple emollient cream, in the treatment of retinoid dermatitis in patients with mild-to-moderate acne.

Methods. This was a prospective, multicenter, open-label, non-randomized, parallel-group study. Patients (age 12-49 years; skin phototype I-IV) with mild-to-moderate acne, who were treated with a topical retinoid for at least one month and had developed skin irritation were assigned to one of the two following treatments: 0.2% Myrtacine® and 4% vitamin PP (N.=116) or a simple emollient cream (N.=48). Both treatments were administered twice daily, 1-1.5 hours after the application of the topical retinoid. Study endpoints were improvement in signs and symptoms of retinoid dermatitis, global efficacy, reduction in acne severity, overall clinical outcome, patient satisfaction and tolerability.

Results. At day 28, compared with the simple emollient cream, 0.2% Myrtacine® and 4% vitamin PP significantly decreased signs (erythema, dryness/scaling, oedema, and roughness) and symptoms (itching, stinging, burning sensation and discomfort) of retinoid dermatitis (P<0.01). In addition, compared with the simple emollient cream, 0.2% Myrtacine® and 4% vitamin PP decreased acne severity in a significantly greater proportion of patients (P=0.023) and was associated with a better clinical outcome (mild, intermediate, clinically relevant or global improvement; P<0.001). 0.2% Myrtacine® and 4% vitamin PP was also associated with greater patient satisfaction and was better tolerated than the simple emollient cream.

Conclusion. 0.2% Myrtacine® and 4% vitamin PP was effective and well tolerated in the treatment of retinoid dermatitis in patients with mild-to-moderate acne and significantly improved acne severity and overall clinical outcome.

Key words: Acne vulgaris - Retinoids - Dermatitis - Vitamin PP.

Corresponding author: S. Veraldi, Department of Anesthesiology, Intensive Care and Dermatological Sciences, University of Milan, I.R.C.C.S. Foundation, Cà Granda Ospedale Maggiore Policlinico, Via Pace 9, 20122 Milan, Italy. E-mail: stefano.veraldi@unimi.it

Acne is a common, multifactorial, inflammatory disease affecting the pilosebaceous unit. It is usually treated with topical retinoids, antiseptics and antibiotics, and with systemic antibiotics and retinoids. Topical retinoids, such as tretinoin, adapalene and tazarotene, are central for the treatment of mild-to-moderate acne. Comedolytic and anti-comedogenic properties of topical retinoids are well documented. However, the use of topical retinoids is often associated with local irritation (“retinoid dermatitis”), which often reduces patients’ compliance. Topical retinoids are often associated with worsening of acne during the first two-three weeks of therapy. Topical emollient compounds can reduce skin irritation caused by topical retinoids by enhancing the stratum corneum barrier function, and thus can increase tolerability and treatment adherence to topical retinoids.

0.2% Myrtacine® and 4% vitamin PP (pellagra preventing, also named niacin, vitamin B3 and nicotinic acid) is a cosmetic adjuvant to medical therapy for acne. Myrtacine®, a myrtucommulone A- and B-rich ethanolic extract obtained from myrtle leaves,
has shown several pharmacological properties in vitro. This extract inhibited keratinocyte proliferation in a dose-dependent manner, inhibited the growth of Propionibacterium acnes, decreased the synthesis of proinflammatory mediators via the cyclo-oxigenase and lipo-oxigenase pathways and decreased the lipase activity in a dose-dependent manner.6, 7 Vitamin PP has been used both topically and systemically in several inflammatory diseases, including acne.8 Several clinical trials have shown that 4% vitamin PP is an effective and well tolerated treatment for acne.9, 10 Vitamin PP inhibits leukocyte chemotaxis. Furthermore, a peptidoglycan present in the cell membrane of P. acnes stimulates toll-like receptor 2 (TLR-2) on the surface of keratinocytes, leading to activation of a number of proinflammatory cytokines, such as interleukin (IL)-6, IL-8 and IL-12. Vitamin PP inhibits cytokine synthesis in keratinocytes and sebaceous glands by down-regulating TLRs, and Nuclear Factor-Kappa-B (NF-kB) and mitogen-activated protein kinases (MAPK) pathways.11, 12

This study was carried out to evaluate the efficacy and tolerability of 0.2% Myrtacine® + 4% vitamin PP for skin irritation secondary to topical retinoid treatment in patients with mild-to-moderate acne, compared with a simple emollient cream that contained no anti-inflammatory compounds.

Materials and methods

Patients

This observational study included patients aged 12-49 years with mild-to-moderate acne receiving a topical retinoid therapy. Consecutive outpatients were enrolled by 24 Italian dermatologists. Patients had to be on uninterrupted topical retinoid treatment for at least one month before inclusion in the study, and had to suffer from skin irritation at screening. Patients had skin phototype I to IV. Study exclusion criteria were as follows: pregnant or breastfeeding women; women planning pregnancy or having unprotected sexual intercourse; patients with a concomitant skin disease; use of a topical or systemic treatment in the weeks prior to the study that the investigators considered may interfere with evaluation of 0.2% Myrtacine® + 4% vitamin PP skin tolerability; intent to use a topical treatment other than topical retinoids or a systemic acne treatment during the study period; exposure to ultraviolet rays; enrolment in another clinical trial or intent to use an emollient product other than 0.2% Myrtacine® + 4% vitamin PP containing anti-inflammatory active compounds during the study period. Patients were permitted to continue using their routine facial products (make-up, make-up remover, shaving foam, cleansing soap). However, no other emollient or soothing facial product was allowed. Neither any acne medications other than topical retinoids were permitted. All patients provided oral consent.

Interventions

Eligible patients were assigned at a 2:1 ratio to one of the two following groups: retinoid treatment plus 0.2% Myrtacine® and 4% vitamin PP in emulsion (group A) or retinoid treatment plus a simple emollient cream (group B). Either study product (0.2% Myrtacine® + 4% vitamin PP) or simple emollient cream were administered twice a day (morning and evening) on the face, after allowing time for complete absorption of the topical retinoid (1 to 1.5 hours after retinoid application).

Assessments

Each of the 24 investigators evaluated 6 patients, 4 from group A and 2 from group B.

Efficacy assessments

Each patient included in the study was evaluated for efficacy over a four-week period, with scheduled visits at day 0, 14 and 28. At each scheduled visit, an “Investigator’s evaluation questionnaire” and a “Patient’s evaluation questionnaire” were completed.

The efficacy endpoints were: improvement in signs and symptoms of irritation (D0, D14, D28), global assessment of irritation (D0, D14,D28), global efficacy of the tested product, based on signs of irritation (D28), reduction in acne severity (D0, D28), clinical outcome (D28), tolerability and patient satisfaction (D28).

Skin irritation

Signs of irritation were assessed at baseline, by an objective evaluation of skin condition by
Clinical outcome (global response to treatment) was assessed at day 28 on a 6-point scale (-1=worsening; 0=no improvement; 1=mild improvement; 2=intermediate improvement; 3=relevant improvement; 4=global improvement).

Satisfaction
Patient satisfaction and acceptability were also evaluated.

Tolerability
Tolerability was evaluated at day 28 as absence of side effects. Global tolerability of the test product was evaluated by investigators and patients, both using a 4-point scale (0=bad tolerability; 1=poor tolerability; 2=good tolerability; 3=excellent tolerability), using validated Global Assessment tools. For the patients’ assessment, patients’ answers to a

### Table I.—Patient demographics and baseline characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Myrtacine® 0.2% + vitamin PP 4% (N.=116)</th>
<th>Simple emollient cream (N.=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs, mean (SD)</td>
<td>21.7 (5.5)</td>
<td>23.9 (6.7)</td>
</tr>
<tr>
<td>Female, N. (%)</td>
<td>69 (60.0)</td>
<td>29 (60.4)</td>
</tr>
<tr>
<td>Retinoids use, N. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tretinoin</td>
<td>43 (37.1)</td>
<td>20 (41.7)</td>
</tr>
<tr>
<td>Adapalene</td>
<td>38 (32.8)</td>
<td>18 (37.5)</td>
</tr>
<tr>
<td>Topical isotretinoin</td>
<td>30 (25.9)</td>
<td>8 (16.7)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (4.3)</td>
<td>2 (4.2)</td>
</tr>
<tr>
<td>Mean weeks of retinoid use (SD)</td>
<td>5.7 (2.5)</td>
<td>6.0 (2.6)</td>
</tr>
<tr>
<td>Acne severity, N. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>16 (13.8)</td>
<td>13 (27.1)</td>
</tr>
<tr>
<td>Mild-to-moderate</td>
<td>56 (48.3)</td>
<td>22 (45.8)</td>
</tr>
<tr>
<td>Moderate</td>
<td>41 (35.3)</td>
<td>10 (20.8)</td>
</tr>
<tr>
<td>Moderate-to-severe</td>
<td>2 (1.7)</td>
<td>3 (6.3)</td>
</tr>
<tr>
<td>Severe</td>
<td>1 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Global assessment of irritation, N. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>5 (4.3)</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Mild</td>
<td>36 (31.0)</td>
<td>19 (39.6)</td>
</tr>
<tr>
<td>Moderate</td>
<td>66 (56.9)</td>
<td>23 (47.9)</td>
</tr>
<tr>
<td>Severe</td>
<td>9 (7.8)</td>
<td>5 (10.4)</td>
</tr>
<tr>
<td>Mean score (SD)</td>
<td>5.1 (2.0)</td>
<td>4.9 (2.0)</td>
</tr>
</tbody>
</table>

*Assessed on a 7-point scale (0=none; 1=none to mild; 2=mild; 3=mild to moderate; 4=moderate; 5=moderate to severe; 6=severe); bAssessed on an 11-point scale (0–1=none; 2–4=mild; 5–7=moderate; 8–10=severe).
questionnaire were recorded by the investigator and scored on the 4-point scale.

**Statistical analysis**

Patient numbers and scaled scores were summarised using mean, standard deviation, median, quartiles, mean and maximum values. Categorical variables were summarised using frequencies and percentages. Statistical tests used to evaluate between-group differences were: Student’s t test for normally distributed data, Wilcoxon test for non-parametric data, Chi-square or Fisher’s exact test if theoretical number of patients is less than 5, or a Cochran-Mantel-Haenszel test for ordinal variables.

**Results**

**Baseline demographics and clinical characteristics**

A total of 167 patients were enrolled between November, 2011 and January, 2012: 116 patients in the 0.2% Myrtacine® + 4% vitamin PP group (Group A), 48 patients in the group receiving simple emollient cream (Group B); three patients were excluded from the analysis. Patient demographics and baseline characteristics are shown in Table I. The mean age of the patient population was 22.4 years; 98 patients (60.1%) were female and 65 (39.9%) were male. Both groups were comparable in terms of age, gender, retinoid use, acne severity and irritation status. Adapalene, topical isotretinoin and tretinoin were the most commonly prescribed retinoids; patients had been using topical retinoids for a mean 5.8 weeks before enrolment in the trial. Global assessment of irritation at baseline revealed that 55 (33.5%), 89 (54.3%) and 14 (8.5%) patients had mild, moderate and severe irritation, respectively.

**Efficacy**

**Global assessment of irritation**

Global assessment of irritation significantly decreased in the group receiving 0.2% Myrtacine® + 4% vitamin PP, compared with the group receiving simple emollient cream (P<0.05); the difference between the treatments was statistically significant (P<0.05) at day 14 and was sustained through day 28 (Figure 1).

**Signs of irritation**

0.2% Myrtacine® + 4% vitamin PP improved all signs of irritation from baseline to day 28: erythema decreased by 59%, dryness/scaling by 70%, oedema by 78%, roughness by 71% (Figure 2). These improvements were significantly greater than those observed with simple emollient cream: erythema decreased by 37% (P<0.001), dryness/scaling by 43%
Clinical outcome
0.2% Myrtacine® + 4% vitamin PP was associated with a better clinical outcome than a simple emollient cream (P<0.001): at day 28 all patients using 0.2% Myrtacine® + 4% vitamin PP had a positive clinical outcome (mild, intermediate, clinically relevant or global improvement), compared with 78% with simple emollient cream; in the 0.2% Myrtacine® + 4% vitamin PP group, 64% had a clinically relevant or global improvement, compared with 15% who used a simple emollient cream.

Patient satisfaction
0.2% Myrtacine® + 4% vitamin PP provided greater patient satisfaction and acceptability (data not shown). Higher scores were given to 0.2% Myrtacine® + 4% vitamin PP over the simple emollient cream for skin softness, suppleness, comfort, soothing, moisturizing and mattifying (P<0.001 vs. emollient for all comparisons), whereas the simple emollient cream received higher scores for negative characteristics – greasiness and stickiness (P<0.001 vs. 0.2% Myrtacine® + 4% vitamin PP for both comparisons). Patients also judged 0.2% Myrtacine® + 4% vitamin PP higher than the simple emollient cream.
cream in terms of general feeling about the product, ease of application, penetration, effect on skin irritation, and compensatory effect on skin dryness and efficacy on acne lesions (P<0.001 vs. simple emollient cream for all comparisons).

**Tolerability**

0.2% Myrtacine® + 4% vitamin PP was better tolerated than the simple emollient cream. Based on the investigators’ assessment, none of the patients had bad or poor tolerability to 0.2% Myrtacine® + 4% vitamin PP, compared with 8.7% to the simple emollient cream; on the other hand, 71% of patients showed excellent tolerability to 0.2% Myrtacine® + 4% vitamin PP, compared with 24% to the simple emollient cream. 0.2% Myrtacine® + 4% vitamin PP produced a displeasing sensation in 3% of patients (13% of the users of the simple emollient cream reported this sensation) (P=0.022 vs. 0.2% Myrtacine® + 4% vitamin PP).

**Discussion**

This study demonstrates that 0.2% Myrtacine® + 4% vitamin PP was more effective than a simple emollient cream in patients with mild-to-moderate acne: it significantly decreased signs (erythema, dryness/scaling, oedema, and roughness) and symptoms (itching, stinging, burning sensation and discomfort) of retinoid-associated skin irritation, compared with the simple emollient cream. The global efficacy score was also significantly higher for 0.2% Myrtacine® + 4% vitamin PP. A significantly greater proportion of patients using 0.2% Myrtacine® + 4% vitamin PP showed decreased acne severity and a positive global clinical response than did those using the simple emollient cream. Treatment with 0.2% Myrtacine® + 4% vitamin PP was associated with higher patient satisfaction than the simple emollient cream and was well tolerated, as reported both by investigator and patient assessments.

The present study is the first to investigate the combination treatment of Myrtacine® and 4% vitamin PP in acne. Previous studies have examined these compounds separately. To our knowledge, Myrtacine® alone has not been investigated in patients with acne; however, this compound has been shown to have anti-inflammatory, antiproliferative, antibacterial, and antilipase activity *in vitro*. Vitamin PP has been found to be effective in patients with acne in a number of studies. For instance, 4% nicotinamide gel decreased acne severity by 52% and acne lesion count by 60% in a randomized, double-blind, 8-week trial; similarly, 4% nicotinamide in a phospholipid emulsion significantly reduced mean acne lesions from baseline in a randomized, double-blind, 12-week trial. Thus, the reduction in acne severity observed in patients treated with 0.2% Myrtacine® + 4% vitamin PP is consistent with that expected for this combination.

**Conclusions**

A combination of 0.2% Myrtacine® plus 4% vitamin PP appears to be an effective and well tolerated anti-inflammatory agents for the prevention and treatment of retinoid dermatitis, due to its soothing and bacteriostatic actions. In the authors’ opinion, the anti-inflammatory action of Myrtacine® may
be enhanced by combining it with vitamin PP. This combination was not only effective against signs and symptoms of skin irritation, but it also reduced acne severity and provided greater tolerability, and greater patient satisfaction and acceptability than a simple emollient cream.

**Riassunto**

Valutazione clinica dell’efficacia e della tollerabilità di Myrtacine® 0,2% + vitamina PP 4% per la prevenzione e il trattamento della dermatite indotta da retinoidi in pazienti con acne da lieve a intermedia

**Obiettivo.** Il presente studio aveva lo scopo di valutare efficacia e tollerabilità dell’emulsione Myrtacine® 0,2% + vitamina PP 4% rispetto ad una semplice crema emolliente nel trattamento di dermatiti da retinoidi in pazienti con acne lieve o moderata.

**Metodi.** Si descrive uno studio prospettico, multicentrico, aperto, non randomizzato e parallelo.

I pazienti (età 12-49 anni; fototipo della pelle I-IV) con acne lieve o moderata in trattamento con retinoidi topici per almeno un mese e che hanno sviluppato una irritazione alla pelle sono stati assegnati ad uno dei due trattamenti successivi: Myrtacine® 0,2% + vitamina PP 4% (N.=116) oppure una semplice crema emolliente (N.=48). Entrambi gli endpoint studio sono stati i miglioramento dei segni e dei sintomi (prurito, pizzicore, bruciore e disagio cutaneo) del trattamento con Myrtacine® 0,2% + vitamina PP 4% (N.=116) oppure una semplice crema emolliente (N.=48). Entrambi i trattamenti sono stati applicati due volte al giorno, 1-1,5 ore dopo l’applicazione del retinoide topico. Gli endpoint dello studio sono stati il miglioramento dei segni e dei sintomi della dermatite, l’efficacia globale, la riduzione del grado di severità dell’acne, l’esito clinico complessivo, la soddisfazione del paziente e la tollerabilità.

**Risultati.** Al giorno 28, rispetto al trattamento con crema emolliente, il trattamento con Myrtacine® 0,2% + vitamina PP 4% ha dimostrato un miglioramento significativo dei segni (eritema, secchezza/desquamazione, edema e rugosità) e dei sintomi (prurito, pizzicore, bruciore e disagio cutaneo) della dermatite indotta da retinoidi (P<0,01). Inoltre, rispetto all’emolliente base, Myrtacine® 0,2% + vitamina PP 4% ha ridotto la severità dell’acne in una proporzione enormemente significativa dei pazienti (P=0,023) ed è risultata associata a un esito clinico migliore (moderato, intermedio, clinicamente rilevante o miglioramento globale; P<0,001). La combinazione Myrtacine® 0,2% + vitamina PP 4% è risultata associata a una migliore soddisfazione dei pazienti e meglio tollerata rispetto all’emolliente base.

**Conclusioni.** Myrtacine® 0,2% + vitamina PP 4% è risultato un trattamento effettivo e ben tollerato nelle dermatiti da retinoidi in pazienti con acne lieve-moderata riducendo significativamente la severità dell’acne e migliorando l’esito clinico complessivo.

**Parole chiave:** Acne - Retinoidi - Dermatite - Vitamina PP

**References**


**Acknowledgements.** The authors would like to thank Yihey Syed and Mary Hines of inScience Communications, Springer Healthcare, who provided medical writing support funded by Pierre-Fabre. The authors would also like to thank: A. Piccirillo, Potenza; L. Francesconi, Catania; P. Del Secco, Udine; G. Alessandrin, Lecce; M. Barbarechi, Milano; J. Sinagra, Roma; P. Broganeli, Torino; C. Cardinali, Prato; N. Gasparini, Terni; F. Kokelj, Trieste; A. Gubbin, Pesaro; D. Piccolo, Pesca; M. Fini, Monza; P. Sena, Bergamo.

**Funding.**—This study was supported by Pierre-Fabre, Milan, Italy. Received on June 22, 2012. Accepted for publication on July 4, 2012.