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ORIGINAL ARTICLE

Efficacy and safety of a 12-month treatment with a combination of hydroxypinacolone retinoate and retinol glycospheres as maintenance therapy in acne patients after oral isotretinoin

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ABSTRACT

BACKGROUND: A correct therapeutic management of acne should include a maintenance therapy to prevent recurrences after discontinuing a successful treatment. The aim of this study is to investigate efficacy and safety of a 12-month maintenance treatment with a product, based on Retinsphere technology that combines retinol encapsulated in glycospheres and hydroxypinacolone retinoate (Biretix gel®), to control acne relapse after a treatment with oral isotretinoin (O.I.).
METHODS: The study consisted of 2 phases: active treatment phase (AP) and maintenance phase (MP). In the AP, 40 consecutive patients with moderate facial acne were treated with O.I. until acne remission. Then, the patients entered in the MP and were treated with Biretix gel® once-daily for 12 months. The efficacy parameter was the relapse rate during MP.
RESULTS: Thirty-nine patients completed the study. Relapse appeared in 6 patients (15.38%). The new product with Retinsphere technology was well tolerated and none of the subjects complained of adverse events.
CONCLUSIONS: Our findings seems to provide favorable evidence of the efficacy and the safety of this new product in the maintenance treatment after O.I. in patient with moderate acne. The efficacy is maintain for a period as long as a year after O.I. suspension.

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Acne vulgaris, because of its long duration and recurring nature, can be defined a chronic disease. In accordance with the US Center for Disease Control the definition of "chronic" identifies a disease "that in general terms, has a prolonged course, does not resolve spontaneously, and for which a complete cure is rarely achieved".[1]

Acne relapses have a negative psychological impact on patients, as they feel incapable of controlling the disease and of reaching complete and persistent healing. Maintenance therapy is necessary in order to maintain acne remission, achieved with an initial successful treatment regimen, and to minimize the risk of relapse.[2]

A widely accepted definition of maintenance therapy is still lacking. As a matter of fact, current guidelines do not indicate if maintenance therapy should begin only after complete clearance of acne or if different levels of improvement may be considered acceptable for starting

a maintenance treatment. Moreover, both actual goals and duration of maintenance therapy should be formally defined.

Currently, topical retinoids represent a rational choice for maintenance therapy.[2, 3] Topical retinoids, by exerting comedolytic and anticomedogenic actions, have been shown to resolve existing non-inflammatory acne lesions, open and closed comedones, and prevent the development of microcomedones.[4-6] In addition, some retinoids, namely adapalene, tretinoin and tazarotene, exert an anti-inflammatory effect, providing therapeutic benefit even on inflammatory lesions.[7-10] On the other side topical retinoids can be associated with skin irritation.[11, 12]

Recently a product, Biretix gel® (Industrial Farmaceutica Cantabria SA, Madrid, Spain), has been used to treat active acne.[13] This new product is based on Retinsphere technology, which combines 2 topical retinoids, retinol encapsulated in glycospheres and hydroxypinacolone retinoate. The hydroxypinacolone retinoate is an ester of all trans-retinoic acid that binds directly to retinoic acid receptors unlike retinol and other derivatives that need to be converted to the biologically active form of retinoic acid.

This combination seems to be able to reduce acne lesions count and follicular keratinization with few and mild side effects.[11] The mechanism of action seems to be similar to tretinoin but with lower grade of irritation in comparison with this retinoid. For this reason, it could be a good candidate as maintenance treatment in acne, as alternative to other retinoids.

The present study was designed to investigate efficacy and safety of a 12-month maintenance treatment with Biretix gel® to control acne relapse after successful treatment with oral isotretinoin (O.I.).

Material and methods

The study was a single-center, open-label, prospective cohort, non-comparative study consisting of two phases: active treatment phase (AP) and maintenance phase (MP).

In the AP, 40 consecutive patients with moderate facial acne were treated with O.I. administered with a drug-sparing alternative treatment regimen, as previously reported, until acne remission.[14] According to the Leeds Grading Scale, patients with acne scores between 0.5 and 3 (corresponding to ≤20 comedones, 10-50 papules and pustules, no nodular or cystic lesions) were considered to have moderate acne.[15, 16]

Only acne patients with a chronic clinical course, who had not responded to previous conventional antibiotic therapy or who had relapsed after discontinuation of antibiotic treatment, were included to receive O.I. Patients were excluded from the study in the presence of other dermatologic conditions requiring interfering treatments, hypersensitivity to any component of the study drugs, pregnancy and breast-feeding.

Liver function tests and lipid profiles were evaluated for all patients before treatment initiation and at 6 weeks after beginning the treatment, and repeated again every 12 weeks, and in addition if needed. Pregnancy tests were carried out one month before treatment, monthly while on treatment, and one month after treatment discontinuation in female patients of child-bearing potential. Oral contraception was started one month before the beginning of the treatment and continued for 4 weeks post-therapy.

Acne patients were treated with O.I., receiving an initial daily dose ≤0.2 mg/kg, in order to reduce the potential for acne flare occurrence, as previously shown.[17] The dosage was subsequently increased by 5 mg every 2 weeks, until the highest dose tolerated by the patient was reached. All patients were treated until complete acne clearing, and for a further month. Decrease of the acne grade to 0.1 and disappearance of all lesions was regarded as complete healing. Then, O.I. was discontinued regardless of the total cumulative dose reached.[12]

The use of a gentle skin cleanser and of moisturizers was encouraged.

Two weeks after O.I. withdrawal, patients entered in the MP. They were treated with Biretix gel® once-daily for 12 months to maintain acne remission and prevent new lesions.

During maintenance treatment, the following data were assessed every 12 weeks: 1) facial acne severity using the Leeds Grading System; 2) clinical side-effects; 3) patient satisfaction with the outcome of care.

Across both study phases, all the patients were assessed by the same physician each time. Patients were required to contact our department in case of self-assessed acne deterioration. If this was the case, a visit was scheduled to calculate acne grade.

In agreement with our previous studies, "relapse" was defined as the emergence of acne ≥0.5 grade se-

verity (corresponding to at least 10 comedones and 10 papules and pustules, or any nodular or cystic lesion [16]) and/or requiring a systemic treatment.

The efficacy variable was the relapse rate at the end of the MP. Safety and tolerability were assessed through evaluations of local skin tolerability and adverse events.

Results

Forty patients (21 males, 19 females, mean age 19.75 years, range 13-44) affected by moderate facial acne were enrolled in the AP. All the patients completed the O.I. treatment achieving acne remission. The mean cumulative dose received by the patients was 77.19 mg/kg (range 29-127.20).

All the 40 patients entered in the MP with Biretix gel®. Throughout the 12-month MP, one patient was lost to follow-up.

In the 12-month MP, relapse appeared in 6 patients (4 male and 2 female, mean age 16.30 years), which corresponds to 15.38% of the population who completed the study. No predictive factors of relapse have been found. Ten patients (25.64%) complained the appearance of acne lesions which, however, did not achieve a severity consistent with the protocol-defined relapse. These patients were treated adding a daily application of topical clindamycin to the 2 retinoid combinations for 12 weeks achieving a significant reduction of acne lesions.

The product with Retinsphere technology was well tolerated and none of the subjects complained of significant local adverse events.

Discussion

Oral isotretinoin is the most widely used medications as it targets all levels of acne pathogenesis. According to expert consensus, the recommended dose is 0.5 mg/kg/day until reaching a mean total cumulative dose of 120-150 mg/kg for severe cases of acne. However, as we have previous reported, lower cumulative dose of O.I. is able to achieve a complete and stable acne remission in patients with mild-to-moderate acne.[14]

Regardless of the dosage regimen used, recurrence of acne lesions following O.I. treatment remains an unsolved problem. According to recent studies, the percentage of patients with relapses without any maintenance therapy is very variable and ranges between 15 and 52% depending on the cumulative and mean daily dose, population characteristics, acne severity and the duration of follow-up (Table I).[18-34] In a previous study young age (≤20 years) and facial grade greater than 3 were predictive of relapse, whereas the effect of both cumulative and mean daily dose of O.I. on relapse rate is still matter of debate.[22, 33]

TABLE I.—*Data on percentage of acne recurrences after oral isotretinoin without maintenance therapy.*

Study	N. patients	Follow-up	Rate of relapse
Chivot *et al*.[19]	172	12-41 months	21%
Layton *et al*.[20]	88	10 years	23%
Stainforth *et al*.[21]	299	5 years	22.7%
Lehucher-Ceyrac *et al*.[22]	237	5 years	48%
Bettoli *et al*.[23]	32		22%
Azoulay *et al*.[25]	17 351		41%
Liu *et al*.[26]	405	2 years	23.2%
Quéreux *et al*.[27]	52		52%
Haryati *et al*.[29]	240		20.8%
Ghalamkarpour *et al*.[30]	83	8.7 months	19%
Morales-Cardona *et al*.[31]	142	24 months	15%
Ghaffarpour *et al*.[32]	132	1.28 years	18.35%
Blasiak *et al*.[33]	180	12 months	32.7%
Coloe *et al*.[34]	102	1 years	45.1%

Unfortunately the studies are based on different designs, different number of patients enrolled and different duration of the follow-up period. Moreover, a definition of recurrence is either lacking or different. As a consequence, consistent conclusions cannot be reached by comparing the above-mentioned studies.

To establish a basis for comparison of the mean relapse rate, the study with the greatest number of patients which described a mean relapse rate of 41%, can be taken into consideration.[25]

Several studies have investigated the efficacy of maintenance therapy in controlling acne relapse after successful initial treatments. Previously available data on acne maintenance therapy consist mainly in topical retinoid in monotherapy used for 12-24-week treatment courses. In most of these studies the maintenance phase with a topical retinoid follows classical combination therapies with topical retinoid, BPO and topical or systemic antibiotics. In only 3 studies the maintenance therapy with topical retinoid follows O.I.

Vender and Vender published a double-blinded, vehicle-controlled proof of concept study investigating the recurrence of acne lesions using tretinoin gel 0.04% after O.I. in a small group of patients.[35] At the end of

the 24 weeks of maintenance treatment the group applying the active agent (7 patients) presented a mean acne lesion count of 1.2. The vehicle group (8 patients) presented a mean lesion count of 3.1, corresponding to a 38% difference.

In the past, we have tested the efficacy of adapalene 0.1% cream as a maintenance therapy after acne remission obtained with an O.I. treatment course in two open-label prospective non-randomized studies. In the first study, 74 patients affected with moderate to severe acne were treated with adapalene 0.1% cream in a 12-month maintenance therapy and then followed up for a further 6 months without treatment.[36] In the second study, 139 patients affected with mild to moderate acne treated with O.I. until complete recovery and for a further month of treatment, underwent a 12-month maintenance therapy with adapalene 0.1% cream.[14] In both studies, as in the present one, a "relapse" was defined as the emergence of acne ≥0.5 grade severity, in accordance with Leeds Grading Scale,[15] and/or requiring a systemic treatment. The rates of acne recurrence observed were 6.7% and 9.35%, respectively.

In 2 studies the fixed-combination adapalene-BPO has been used as maintenance therapy: in one study after classical therapy whereas in another study the authors used it after O.I.[37, 38] In that study, among the 68 patients who remained in the MP only 2 patients (2.94%) experienced a relapse.[38]

Recently Truchuelo *et al.* have assessed the efficacy and the safety of Biretix gel® in controlling the number of relapse following O.I. treatment in a prospective, randomized, double-blind, vehicle-controlled and split-face study involving 30 acne patients.[11] The active product was applied to one side of the face and the vehicle to the other, once daily for 3 months. Relapse has been defined as the occurrence of at least one acne lesion in addition to the clinical condition present before O.I. At the end of the treatment, the vehicle side showed a relapse rate of 43%, similar to that observed in the literature in the follow-up of groups without post-isotretinoin treatment.[25] The side treated with Biretix gel® showed a significantly lower relapse rate (17%), demonstrating the efficacy of maintenance treatment with this topical. No adverse events and an excellent tolerability was also demonstrated. In this study the time between stop O.I. and the start with the topical treatment was very variable, ranging from 2 weeks to 6 months.

In the present study among the 39 patients who remained in the MP with daily application of Biretix gel® only 6 patients (15.38%) experienced a protocol-defined relapse. The small number of patients lost to follow-up suggests a high adherence to this long-term maintenance protocol among our studied patients. Nevertheless, adherence to daily treatment was not objectively assessed.

The main limitation of our study is its observational design, lacking of an age-, sex- and acne severity-matched control group.

The different design of the two studies evaluating Biretix gel® as maintenance therapy following O.I., the different definition of "relapse" and the different duration of the maintenance phase make difficult to compare the results.

Conclusions

Avoidance of a relapse after treatment with O.I. is an important step in the treatment of a chronic disease as acne. How to avoid the relapse has not been studied in depth and many questions are still unsolved: how can we define maintenance therapy? What should be the duration of maintenance therapy? When should it be started?

The use of topical retinoids after O.I. suspension appears to be a protective factor to prevent relapse, with efficacy and tolerability demonstrated in previous studies.

Biretix gel® has been already proven to be effective and safe in the maintenance period as long as 3 months.

Our findings confirm the efficacy of this product based on Retinsphere technology in the maintenance treatment after O.I. in patient with moderate acne. Efficacy is maintained for a period of a year after O.I. suspension. The good tolerability makes the patients able to start this topical vitamin A derivate combination 2 weeks after O.I. discontinuation and to use it over a long period.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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