Combination of Acitretin and Oral Calcitriol for Treatment of Plaque-type Psoriasis

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Sir,

Combination treatment has been the basis of the management of psoriasis, especially when treating moderate-to-severe disease (1). Rotational therapy has also demonstrated its utility in psoriasis (1).

The effectiveness of acitretin has been demonstrated in the treatment of psoriasis (2). Its effectiveness in monotherapy is low and it is usually administered in combination with other topical or systemic treatments in order to obtain faster whitening with fewer secondary effects. It has been used in combination with vitamin D derivates applied topically (3, 4) with psoralen ultraviolet A therapy (PUVA) and UVB phototherapy, and with methotrexate and cyclosporine (5).

Recently, combinations of biologics with acitretin have also been shown to be of some benefit (6).

There are publications that confirm the effectiveness of oral calcitriol in the treatment of plaque-type psoriasis and arthropathic psoriasis (7–9). The effects of topical vitamin D and its derivates are widely known and are the basis of the maintenance treatment for stable plaque-type psoriasis (7).

The objective of this open study was to determine the effectiveness of the association between oral calcitriol and acitretin in patients with plaque-type psoriasis.

MATERIALS AND METHODS

Study design

A prospective randomized study was performed with 2 groups of patients: one group received acitretin (Neotigason®, Roche, Spain) at an initial dosage of 25 mg per day for 45 days and 25 mg every other day for an additional 45 days. The other group was treated for 90 days with a combination of acitretin (Roceltrol®, Roche, Spain) at the same daily dosage and calcitriol 0.25 μg/day. The acitretin dosage varied from 0.25 to 0.4 mg/kg, with no differences between the 2 groups.

The Psoriasis Area and Severity Index (PASI) was measured by the same investigator (MSR) at the beginning of the study and at day 90 on completion of the study. All adverse events were recorded. A complete blood count, hepatic and renal function, and calcaemia were recorded at every visit, as was excretion of calcium in 24-h urine.

Inclusion criteria

Plaque-type psoriasis with a PASI of between 15 and 40, and age older than 18 years.

Exclusion criteria

Illnesses for which treatment with acitretin is contraindicated (hyperlipidaemia, hepatic insufficiency). Illnesses for which treatment with calcitriol is contraindicated (hypercalcaemia, disorders of the thyroid and parathyroid gland, history of renal calculi). Women of reproductive age who had received topical or systemic treatment in the 2 or 6 weeks, respectively, prior to the study.

Statistical analysis

Statistical analysis with SAS v.8 software, using multivariate analysis of variance (MANOVA) was performed, with $p < 0.05$ regarded as significant.

RESULTS

A total of 40 patients with plaque-type psoriasis (21 females, 19 males; median age 61 years, age range 48–76 years, median weight 74 kg, range 62–89 kg) were enrolled in the study. Patients were divided randomly into 2 groups, one receiving acitretin and the other acitretin and calcitriol. There were no statistically significant demographic differences between the 2 groups. All of the patients completed the study.

Disease severity was assessed at the beginning of the study, at day 45 and at the end of the study. The mean initial PASI was 27.63 (SD 7.77). There were no statistically significant differences in the mean PASI between the 2 groups.

The overall evolution of the PASI is seen in Table I, with stabilization in the last 45 days of treatment. The difference between the PASI at the beginning and at the end of the treatment is statistically significant ($p<0.05$).

Also significant is the difference in PASI evolution between the 2 groups ($p<0.05$).

The most frequent side-effect noted in the patients was xerosis of the skin and lips, which affected 25% of all patients, with no differences between the 2 groups. Secondly, hypercholesterolaemia and hypertriglyceridaemia were observed in up to 15% of all patients, and elevation of the liver enzymes in 10%. These side-effects appeared equally in the 2 groups and in proportion to acitretin intake. In the group treated with

Table I. *PASI in relation to the treatments received. (n=20 in each group)*

	Initial PASI	PASI at day 45	Final PASI (day 90)	Difference between initial and final PASI	*p*
Acitretin+calcitriol	28.35	11.2	10.3	18	<0.05
Acitretin alone	26.90	14.2	13.3	13.6	

PASI: Psoriasis Area and Severity Index.

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calcitriol and acitretin, 10% of the patients exhibited increased calciuria with no other alteration in calcium or phosphorus metabolism or renal function. During the period of study, no adverse events related to this fact were noted, for instance, appearance of a renal colic. One month after the end of the study calcium excretion was recorded again, with normalization in all patients.

DISCUSSION

Combination of therapies is widely practised in treating psoriasis, with the aim of achieving a faster reduction in the PASI and reducing secondary effects. Both calcitriol and acitretin treatments have demonstrated their effectiveness in treating psoriasis, whether alone or in combination with other drugs and phototherapy. However, their effectiveness in combination has not been evaluated previously.

Each of the 2 treatments has a different mechanism of action, and the combination of acitretin and topical calcipotriol has been shown to be more effective than acitretin alone (3, 4).

This study aimed to determine whether the combination of acitretin and oral calcitriol is more effective than using acitretin alone, in terms of reduction in the PASI. The results show a statistically significant difference in PASI evolution between the groups, and suggest that a faster reduction in the PASI can be achieved by combining the treatments than by using acitretin alone.

It is also notable in both groups that in the evolution of the PASI there is a stabilization of the decrease from the 45th day of treatment, suggesting that the greater part of the benefit is exerted in the first month of treatment.

No significant differences in the adverse effects were noted. The majority (xerosis, hypercholesterolaemia, hypertrigliceridaemia) were attributed to the use of acitretin (10). In 10% of the patients, asymptomatic hypercalciuria was detected and was related to the use of calcitriol. No hypercalcaemia was observed. Adverse effects related to hypercalciuria should be followed up, although no one was detected during the study time and it was normalized after a month of clearing-up. With long-term therapy, the risk of renal calculi or renal function impairment should be considered.

Apart from achieving a faster reduction in the PASI, this combination could be of some benefit to patients with psoriasis who, due to the use of acitretin, are at risk of osteopaenia. At the same time, both treatments can reduce skin malignancies in patients with psoriasis who have received high doses of phototherapy. These hypotheses need to be confirmed.

There are several limitations to this study. A larger sample size would be advisable, as well as a longer follow-up to see, for instance, if the reduction in PASI is maintained. The fact that the study is not blinded confers a considerable bias, which, due to the characteristics of the study, could not be avoided.

In conclusion, this study shows a certain benefit obtained from combining oral calcitriol and acitretin: a greater reduction in the PASI. Larger, long-term studies are required to support these results.

Conflicts of interest: No conflict was reported.

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