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CLINICAL REPORT

Low-dose Acitretin in Treatment of Plaque-type Psoriasis: Descriptive Study of Efficacy and Safety

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The efficacy and safety of acitretin was evaluated retrospectively in a cohort of 46 patients with moderate to severe plaque psoriasis (Psoriasis Area and Severity Index (PASI) range 10–42). Patients were treated at an initial dose of 10 mg/day acitretin, which was then gradually increased until the best therapeutic effect with the fewest adverse effects was reached (<50 mg/day) and later decreased and maintained at the lowest effective dosage. Efficacy measures were: (*i*) PASI75 (75% improvement) and PASI50 between 10 and 16 weeks; and (*ii*) PASI75 even after 16 weeks of treatment. At weeks 10–16, PASI75 and PASI50 were achieved by 47.8% and 87% of the patients, respectively. Overall, 67.3% reached PASI75. Adverse events occurred in 18 patients (39.1%); among these, 4 (8.7%) discontinued acitretin. Our findings suggest that acitretin at an initial low, gradually escalating dose, and subsequently maintained at the minimal effective dose, is a suitable treatment option for plaque psoriasis as it provides clear-cut improvement in most treated patients while minimizing the risks of side-effects. *Key words: plaque psoriasis; acitretin; monotherapy; PASI75; side-effects.*

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Acitretin, an aromatic retinoid, has been a valuable option for the treatment of psoriasis since the late 1980s. Retinoids primarily act by normalizing keratinocyte differentiation, thus decreasing epidermal proliferation; moreover, the drug exerts immune-modulatory and anti-inflammatory effects without a direct immunosuppressive effect (1–5). Acitretin has been proven to be effective in psoriasis, both as monotherapy as well as in combination with phototherapy or other systemic agents, without significant loss of efficacy over time (6–9). As monotherapy, acitretin is considered to be more effective in pustular and erythrodermic psoriasis compared with chronic plaque-type psoriasis (8, 9).

The recommended daily dosage of acitretin in monotherapy for patients with plaque-type psoriasis is between 25 and 50 mg (6, 7, 10–12). Although higher doses seem to be more efficacious in terms of clinical improvement in psoriasis, the incidence of acitretin-associated clinical and laboratory adverse events is largely dose-dependent (13). Considering the chronic course of psoriasis, low-dose acitretin (between 25 and 35 mg/day) is preferable as it reduces the risk of adverse events without sacrificing long-term effectiveness (14–16). Some authors suggest starting treatment with a lower daily dosage (between 10 and 25 mg) followed by a gradual dose escalation (9, 17–19).

Apart from its teratogenic and osteogenic potential acitretin is probably the safest of the available systemic agents for long-term use and has not been associated with risk of cancer development. Moreover, most of the adverse effects are largely reversible on discontinuation of the therapy and it rarely causes the cumulative toxicities seen with traditional systemic psoriasis treatments (8, 9, 13, 14).

Hence, acitretin could continue to have an important role in the treatment of psoriasis even in the biologic era. In spite of this, acitretin is not suggested in Europe as a first choice for monotherapy among the conventional systemic treatments (20).

The main aim of this study was to retrospectively evaluate efficacy and safety of acitretin as monotherapy in a historical cohort of patients with moderate to severe plaque psoriasis, on a low daily dose, long-term regimen. Furthermore, possible demographic and clinical risk factors predicting treatment failure or intolerance to acitretin were investigated.

MATERIALS AND METHODS

Study design and objectives

A mono-centric, retrospective, non-comparative study was conducted on a cohort of patients affected by plaque psoriasis, who were treated with acitretin monotherapy between January 2006 and September 2013 at the Psoriasis Outpatient Unit of the Dermatology Section of the University of Ferrara, Italy.

The aims of the study were: (*i*) to assess the efficacy of acitretin as monotherapy administered at low daily dosage on an initial stepwise escalating regimen in the treatment of moderate to severe plaque psoriasis; (*ii*) to assess the safety of the treatment; (*iii*) to assess prognostic significance of demographic and clinical features, as potential risk factors for treatment failure or inducing side-effects.

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Study patients

In our clinical practice during the study period, patients were eligible for acitretin treatment if they were ≥ 18 years of age and affected with plaque psoriasis with a PASI ≥ 10 or with other severe types of psoriasis (erythrodermic and pustular psoriasis). Exclusion criteria for acitretin treatment were: severe renal or hepatic dysfunction, hepatitis, pregnancy, breastfeeding, desire to have children, insufficient guarantee of effective contraceptive measures, excessive alcohol abuse, or blood donation. Relative contraindications were: diabetes mellitus, history of pancreatitis, hyperlipidaemia (particularly hypertriglyceridaemia) and drug-controlled hyperlipidaemia, wearing contact lenses, concomitant treatment with drugs potentially interfering with retinoid metabolism or retinoid effects, such as tetracyclines, phenytoin, vitamin A, and antifungal imidazoles. In women of child-bearing age, contraception was recommended during treatment and up to 2 years after discontinuation of therapy. Acitretin was not indicated in the treatment of psoriatic arthritis except in cases of minimal articular involvement.

For the objectives of the present study, patients were excluded from the retrospective analysis in the presence of: prescription of acitretin in combination with topical calcipotriol, photo(chemo) therapy, other systemic, either conventional or biological, treatments; pustular psoriasis; articular involvement requiring treatments potentially active on skin psoriasis; treatment with other systemic therapies during the 4 weeks preceding acitretin administration; incompleteness of any data necessary for our analysis.

Forty-six patients fulfilled the inclusion criteria. Eleven psoriatic patients treated with acitretin during the analysed period were excluded from the study as they failed to meet eligibility criteria.

Laboratory and clinic controls were carried out before and during the treatment according to guidelines (8, 20).

Data collection

A standardized data collection form was elaborated to collect the following data from the hospital clinical records: (*i*) patients' demographics, weight and height, waist circumference, laboratory values before and during treatment, (*ii*) comorbidities, (*iii*) lifelong history of the psoriasis, recorded as the time (in years) between disease onset and starting acitretin treatment, (*iv*) previous systemic treatments, (*v*) disease severity before starting and throughout acitretin treatment evaluated by the PASI, (*vi*) mean daily dosage of acitretin, (*vii*) duration of treatment, in months, (*viii*) duration of treatment response (PASI75), in months, (*ix*) drug-related adverse effects, (*x*) reason for treatment withdrawal. If a patient had received more than one course of acitretin during the nearly 8-year period, only the last treatment was considered. Metabolic syndrome was diagnosed according to the revised National Cholesterol Education Program (NCEP) Adult Treatment Panel III criteria (21).

Study procedures and assessment

Patients started treatment with 10 mg/day acitretin (Neotigason, Actavis Italy S. p.A., Nerviano (MI), Italy), increasing daily dosage of 10 mg every 2 weeks until achieving the best therapeutic effect with the fewest adverse effects (minimal effective dose), without exceeding 50 mg/day. Then, if possible, daily dosage was decreased stepwise and a maintenance dose that was tolerated by the individual patient and had sufficient efficacy was administered. The duration of maintenance treatment depended on improvement and tolerance in the individual patient. Throughout the treatment duration, additional local moisturizing or emollient products expected to hydrate the affected skin and to relieve itching were allowed.

In conformity with the data available from clinical trials and guidelines (20), the primary measure for clinical efficacy was the rate of patients achieving the PASI75 response between 10 and 16 weeks after beginning the treatment, which corresponds to an improvement from baseline in the PASI of ≥ 75%. Secondary outcome measure was the rate of patients achieving at least an improvement from baseline in the PASI of ≥ 50% (PASI50). The tertiary efficacy end-point was the rate of patients reaching a PASI75 response, albeit after 16 weeks of treatment; in which case we recorded the weeks necessary for achieving the clinical response. Moreover, we assessed the period of response during treatment, considered as the months in which patients maintained a PASI75 response before stopping treatment.

Objective patient assessment was performed by the same investigators at baseline and at the 8–12-week control visit across the entire treatment.

Adverse events and their causal relationship to acitretin were assessed. We were also interested in reviewing the rate of patients who discontinued the treatment due to development of drug-induced side-effects.

The following demographics and clinical features of the included subjects were statistically elaborated in order to identify factors potentially predisposing to treatment failure or development of side-effects: patients' demography, BMI, duration of psoriasis before starting acitretin, disease severity at baseline, mean daily dosage of acitretin. In patients reaching PASI75, we assessed if patient age, duration of psoriasis before starting treatment, disease severity at baseline, mean daily dosage of acitretin were associated with rapid (at 10–16 weeks of treatment) or late (after 16 weeks) achievement of disease response (PASI75).

Statistical analyses

Categorical data are presented as numbers and percentages. All results are shown as arithmetic mean ± standard deviation (SD). Binary data were analysed with χ^2 or Fisher exact test according to conditions. Quantitative data were analysed by means of *t*-test, in case of normality and homoscedasticity, or, alternatively, by means of Mann-Whitney *U* test. Normality of groups was assessed by Kolmogorov-Smirnov test; homoscedasticity of groups was assessed by Levene's test and Brown-Forsythe test. A p-value < 0.05 was considered as statistically significant.

RESULTS

Patient characteristics

Demographic and clinical data of the 46 patients affected with plaque psoriasis who entered the study are reported in Table I. At the time of starting acitretin therapy, the mean PASI score was 20.3 (range 10.0–41.4). Combined presence of at least 3 of the comorbid conditions representing the metabolic syndrome was found in 9 patients (19.6%). Acitretin was administered for a mean of 15.0 months (range 1–79 months); the mean daily dose during treatment was 22.5 mg (range 5.2–48.9 mg).

Efficacy evaluations

At the time of data collection, 13 patients (28.3%) were still on acitretin treatment, while 33 patients (71.7%) had discontinued treatment due to: achievement of clinical response (PASI75) without adverse events and discontinuation of any treatment (6 patients,

Table I. *Baseline demographic and clinical features of the study patients, with comparisons between responder and non-responder patients*

	Total	Responders[a]	Non-responders
Patients, *n* (%)	46 (100)	31 (67.4)	15 (32.6)
Males	35	22	13
Females	11	9	2
Age, years, mean ± standard deviation (SD) (range)	61.4 ± 15.3 (28–90)	60.8 ± 15.9 (35–90)	62.7 ± 14.5 (28–80)
Psoriasis Area and Severity Index score, mean ± SD (range)	20.3 ± 7.8 (10–41.4)	21.0 ± 7.5 (10.0–41.4)	18.7 ± 8.3 (10.1–33.4)
Disease duration, years, mean ± SD (range)	19.25 ± 10.6 (0.5–42)	17.3 ± 11.2 (0.5–42)	23.2 ± 8.5 (12–39)
Previous systemic treatments, patients, *n* (%)	22 (47.8)	14	8
Body mass index, kg/m^2, mean ± SD (range)	27.5 ± 4.3 (22–42.9)	26.9 ± 3.2 (22–36)	28.63 ± 6 (23–42.9)
Dose, mg/day) mean ± SD (range)	22.5 ± 9.3 (5.2–48.9)	22.2 ± 8.4 (10.6–46.4)	23.2 ± 9.8 (5.2–48.9)
Metabolic syndrome, patients, *n* (%)	9 (19.5)	6	3
Major comorbidities, patients, *n* (%)	17 (36.9)	11	6
HIV	2 (4.4)	1	1
Cancer	7 (15.2)	4	3
Chronic obstructive pulmonary disease	4 (8.7)	4	0
Chronic renal failure	3 (6.5)	2	1
Previous tuberculosis	1 (2.2)	0	1

[a]Responders were patients who reached PASI75 at any time during the treatment.

13.0%); completion of scheduled course of treatment until disease improvement and subsequent switch to other maintenance therapies, namely topical agents or phototherapy (6 patients, 13.0%); poor tolerability (4 patients, 8.7%); response considered unsatisfactory by the physician and/or by the patient (9 patients, 15%); loss of efficacy or psoriasis recrudescence (> 50% increase in baseline PASI score) after achievement of clinical response (3 patients, 6.5%); occurrence of diseases not related to psoriasis requiring hospitalization and/or treatment withdrawal (2 patients, 4.3%). Three patients (6.5%) were lost to follow-up due to change of residence.

Regardless of the reasons for acitretin discontinuation, at week 10–16 the PASI75 response (primary efficacy end-point) was achieved by 22 out of 46 treated patients (47.8%). The overall efficacy results are summarized in Table II.

Six patients (66.7%) among those (9 patients) who discontinued treatment due to a response considered unsatisfactory, in any case reached PASI50.

In patients achieving PASI75, disease response was maintained during treatment from 1 to 77 months (mean 14.1 months), which corresponded in percentage to 12.5–100% (mean 94.2%) of the subsequent treatment duration. Twenty-three (74.2%) patients among those achieving PASI75 maintained it along the entire subsequent treatment duration.

Safety evaluation

During the entire study, 18 patients (39.1%) experienced clinical and/or biochemical adverse events induced by acitretin (Table III). In most cases adverse events were mild and tolerable and did not require interruption of therapy. Adverse effects were usually managed by reducing daily dosage or, in other cases, resolved with continued treatment thus indicating development of tolerance. Four patients (8.7%) were required to discontinue acitretin due to occurrence of side-effects potentially related to the treatment, including depression, headache, myalgia and hair loss. In all patients followed after discontinuation of acitretin, drug-induced clinical and/or biochemical adverse events reversed within a few weeks after discontinuing acitretin.

Table II. *Efficacy parameters*

Psoriasis Area and Severity Index (PASI)	10–16 weeks *n* (%)	> 16 weeks *n* (%)	Total *n* (%)
PASI75	22 (47.8)	9 (19.6)	31 (67.4)
PASI50	40 (87.0)	1 (2.1)	41 (89.1)

Demographic and clinical predicting factors for treatment outcome and side-effects

Demographics and clinical data of responding (PASI75 at any moment of treatment) and non-responding patients are reported in Table I. Neither age at baseline ($p = 0.694$, *t*-test), nor gender ($p = 0.296$, Fisher's test), nor BMI ($p = 0.542$, Mann-Whitney *U* test), nor PASI

Table III. *Incidence of adverse events during treatment*

Adverse events	Patients (%)
Alopecia	6 (13.0)
Xerophthalmia	5 (10.9)
Cheilitis	5 (10.9)
Fatigue	5 (10.9)
Gastrointestinal disorders	4 (8.7)
Hyperlipidaemia	4 (8.7)
Reduced vision	3 (6.5)
Increase bilirubin	2 (4.4)
Irritability	2 (4.4)
Tremor	2 (4.4)
Myalgia	2 (4.4)
Depression	1 (2.2)
Increased gamma-glutamyltransferase	1 (2.2)
Increased transaminase	1 (2.2)
Photosensitivity	1 (2.2)
Patients with at least one adverse event	18 (39.1)

score before starting treatment ($p = 0.385$, *t*-test), nor mean acitretin daily dose over treatment ($p = 0.717$, *t*-test) were found to significantly relate to treatment failure in our population. Only longer duration of psoriasis before entering the study was found to be related to treatment failure in an almost significant way ($p = 0.075$, *t*-test). There was no association between speed of response and the following factors: age at baseline ($p = 0.702$, *t*-test), gender ($p = 0.384$, Fisher's test), duration of psoriasis before treatment ($p = 0.102$, *t*-test), PASI score before starting treatment ($p = 0.765$, *t*-test), and mean daily acitretin dosage ($p = 0.770$, *t*-test). Patients' demographic and clinical data were analysed to predict the development of side-effects. There was no correlation with incidence of side-effects of: age at baseline ($p = 0.616$, *t*-test), gender ($p = 0.560$, Fisher's test), or mean daily acitretin dosage ($p = 0.926$, *t*-test).

DISCUSSION

The results of this study showed a substantial efficacy of the analysed long-term (mean duration 15.0 months), low-dose (mean 22.5 mg/day), and low starting dose (10 mg/day) acitretin regimen in moderate to severe psoriasis (baseline mean PASI 20.3). In fact, at weeks 10–16, PASI75 was achieved by almost half of the patients, while 87.0% reached PASI50. These findings are difficult to compare with those of most other published studies assessing the efficacy of acitretin because varying definitions of therapeutic success as well as inhomogeneous study populations and treatment regimens have been used (7, 16, 17, 22–24). However, our results are similar to those of other reports using the now widely accepted PASI75 and PASI50 efficacy criteria, even where higher daily doses were used than in our study (8, 14). It is noteworthy that more than 67% of patients reached PASI75 during the whole study period. According to several authors, acitretin induces a gradual improvement in psoriasis in many cases requiring more than 3–4 months for a full response (8, 9, 19, 20). Thus, assessment after 10–16 weeks is likely to have underestimated the efficacy of acitretin in this and previous studies. Indeed, our findings suggest that acitretin monotherapy is eventually effective in a considerable percentage of patients with plaque-type psoriasis. Moreover, once attained, disease response was maintained in most patients during the subsequent acitretin treatment. Among the analysed demographic and clinical features, only a longer duration of the disease before starting acitretin was found to correlate with treatment failure in an almost significant way ($p = 0.075$).

Common adverse effects observed in our study were mucocutaneous, including dry skin and mucous membranes and hair loss. Non-specific headaches, gastric symptoms, particularly stomach pain and nausea, blurred vision, photosensitivity, asthenia, bone and muscle pain, hands or feet trembling, irritability were also reported. A case of depression was diagnosed, even though a true association with acitretin remained doubtful. These adverse effects were always reversible and only required symptomatic treatment or a temporary dose reduction of acitretin; in only 4 cases (8.7%) treatment was withdrawn due to clinical adverse events. Furthermore, in some individuals acitretin increased the serum triglyceride levels, as in previous studies (7–9, 20). However, in our study cohort only a few patients (15.2%) developed laboratory anomalies that did not require discontinuation of acitretin therapy. No particular demographic or clinical features were found to be associated with the development of side-effects.

The rate of occurrence of adverse events in our study was lower than in other reported experiences (23, 25–28). The very low starting dose and the low mean daily dosage administered in our population may account for this finding, as the incidence of acitretin-associated clinical and laboratory adverse events has been shown to be largely dose dependent (8, 9, 13).

The main limitation of this study is the lack of an age- and psoriasis severity-matched control group. The relatively small number of patients studied ($n = 46$) and the retrospective nature of our survey represent further limitations. As in a certain number of study patients rotational therapy with other treatments has been scheduled, the mean duration of disease remission after acitretin discontinuation has not been evaluated.

In conclusion, due to the need for prolonged, and usually life-long, therapy of patients with psoriasis, our experience indicates that acitretin is a suitable treatment option, as it results in clearing in most patients while minimizing the risk of side-effects and toxicities. Based on our findings, a low initial dosage, escalating stepwise is recommended; once the minimal effective dose has been achieved it is possible to reduce the dose slightly in order to maintain clinical efficacy and improve tolerance long-term.

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