Effectiveness and Safety of Acitretin in Children with Plaque Psoriasis: A Multicenter Retrospective Analysis

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Abstract

Background: Acitretin is licensed for and is most commonly used to treat psoriasis. Little information exists about its efficacy and safety in childhood and adolescent psoriasis.

Methods: Retrospective analysis of a group of children and adolescents (<17 years of age) with moderate to severe plaque psoriasis treated with acitretin between 2010 and 2014 at Italian dermatology clinics. Patients were identified through databases or registries.

Results: The study population consisted of 18 patients with a median age of 9.5 years at the start of therapy. The median maintenance dosage per day was 0.41 mg/kg. Eight patients (44.4%) achieved complete clearance or good improvement of their psoriasis, defined as improvement from baseline of 75% or more on the Psoriasis Area and Severity Index at week 16. Three had three or more courses of treatment with short disease-free intervals. In three patients, acitretin treatment was ongoing at the time of data collection. The mean total duration of treatment in responders was 22.7 months. One patient discontinued
treatment because of arthralgia. The remaining nine patients (50%) discontinued treatment because it was ineffective. Mucocutaneous adverse effects occurred in all patients, but did not affect therapy maintenance.

**Conclusions:** In this retrospective case series, acitretin was a moderately effective, well-tolerated treatment in children with moderate to severe plaque psoriasis. Given the small number of patients, statements about long-term safety are not possible.

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**INTRODUCTION**

Psoriasis is a common inflammatory skin disease that starts in approximately 30% of patients before adulthood (1,2). Its prevalence in childhood is unknown, but it has been estimated to range from 0.1% to 3% (2,3). Incidence rates in children have more than doubled since 1970 (4). In children, psoriasis usually follows a benign course and is often successfully managed with topical agents. Nevertheless, moderate or severe forms of the disease may be unresponsive to topical therapy and require more aggressive approaches, including phototherapy and systemic drugs. For the most part, systemic therapies have not been thoroughly investigated in childhood plaque psoriasis. Beneficial effects of systemic drugs have been assumed because of clinical evidence and experience in adults (1). Consequently, there are no international standardized guidelines for medical treatment of moderate to severe childhood psoriasis, and there is a substantial unmet need for treatment options in patients recalcitrant to topical therapy or phototherapy.

Acitretin, an active metabolite of etretinate, is the most widely used systemic retinoid in the treatment of psoriasis (5). It is efficacious as monotherapy in some clinical subtypes of psoriasis, specifically pustular and erythrodermic psoriasis. Although there is extensive literature on and experience using acitretin in children with genetic disorders of keratinization, data on its efficacy and safety in plaque psoriasis are scarce (6,7). In this study, we aimed to expand current knowledge regarding the use of acitretin in childhood psoriasis by assessing its effectiveness and short-term safety in 18 children with moderate to severe plaque psoriasis.

**PATIENTS AND METHODS**

**Study Design and Study Population**

This was a multicenter, retrospective, noncomparative study in a cohort of patients with plaque psoriasis. Case records of all consecutive patients younger than 17 years of age who were given oral acitretin for moderate to severe plaque psoriasis from 2010 until 2014 were examined. Moderate to severe chronic plaque psoriasis was defined as a Psoriasis Area and Severity Index (PASI) score of 10 or greater at baseline. The setting was a number of Italian dermatology centers belonging to the Pediatric Dermatology Group of the Italian Society of Dermatology. Patients were identified through databases or registries. Information was collected on sex; age; age at onset of psoriasis; association with psoriatic arthritis and other comorbidities; age at onset of acitretin treatment; previous systemic treatments; disease severity assessment using the PASI before each treatment, after 16 weeks of treatment, and at the end of treatment; duration of treatment; results of routine blood work during treatment; adverse events; reasons for withdrawal or switch; and physician notes.

Only patients younger than 17 years who had all requested data available and who had no concomitant systemic antipsoriatic treatment or phototherapy while they were taking acitretin were considered eligible for this study. At the beginning of the trial, all patients had baseline screening for complete blood count, liver function tests, serum triglycerides and cholesterol, creatine phosphokinase, gamma-glutamyl transpeptidase, total and direct bilirubin, lactate dehydrogenase, and serum uric acid. Laboratory tests were performed at monthly intervals during the first 2 months of treatment, and every other month thereafter. Safety was assessed according to vital signs, physical examination, laboratory tests, and physician and patient evaluation of adverse events occurring during treatment. Effectiveness was assessed according to the proportion of subjects who achieved 75% or greater reduction in baseline PASI score (PASI75) after 16 weeks of therapy. Patients who discontinued therapy before 16 weeks because of a lack of response were considered nonresponders. Concomitant treatment with topical steroids, vitamin D3 ointments, coal tar
preparations, or anthralin was considered acceptable. Descriptive statistics (e.g., percentage, means, standard deviations) were used to summarize the data.

RESULTS

Patient Characteristics

We identified 25 potential subjects younger than 17 years of age with psoriasis who were treated with oral acitretin between January 1, 2010, and December 31, 2014. After screening the complete medical records from all health care providers, 18 patients with moderate to severe plaque psoriasis fulfilled criteria for inclusion in this case series. Six excluded subjects had diagnoses other than plaque psoriasis (e.g., pustular and erythrodermic psoriasis) and one had missing information. Enrolled patients, 12 boys and 6 girls, were ages 1 to 11 years (mean age 7.4 years) at the diagnosis of psoriasis. A positive family history of psoriasis was found in three patients (16.6%). Medical histories included streptococcal recurrent pharyngotonsillitis in two patients, streptococcal perianal dermatitis in one, obesity (as defined according to World Health Organization) in four, and irritable bowel syndrome in one. No history of diabetes, hypertension, or Crohn’s or celiac disease was recorded. Ten patients did not have associated diseases. At commencement of acitretin, patients had a mean age of 9.5 years (range 2–14 years). Three of the six girls were 14 years old. Their parents were advised about the contraindication of acitretin in females of reproductive potential. They signed a patient agreement and informed consent with information about preventing pregnancy while taking acitretin and for at least 3 years after discontinuing the drug. No patients received oral contraceptives during acitretin therapy. All patients were commenced on acitretin for moderate to severe plaque psoriasis recalcitrant to topical treatment, narrowband ultraviolet B (nbUVB), and other systemic treatments. The median baseline PASI score ± standard deviation (SD) was 17.4 ± 7.8. All patients had undergone topical treatment before. Two (11.1%) had been treated with nbUVB and five with cyclosporine; one had also been treated with psoralen UVA. Thus, in 13 patients (72.2%), acitretin had been administered as first-line systemic treatment. Demographic and clinical data of the 18 patients who entered the study are reported in Table 1.

Therapy Dosage

Acitretin was commenced with a dose ranging from 0.2 to 0.5 mg/kg according to the single-centers’ experience. The daily dose was increased to 0.6 mg/kg in two patients after 8 weeks based on clinical response and tolerance. The median maintenance dosage per day was 0.41 ± 0.14 mg/kg.

Treatment Duration

The mean total duration of treatment in responders was 22.7 ± 12.0 months. At the time of data collection, three patients (16.6%) were still under treatment.

Effectiveness, Tolerability, and Safety

Eight patients (44.4%) achieved a PASI75 response at 16 weeks and were classified as responders. Three had histories of previous systemic treatments. The mean baseline PASI score was 17.5 ± 8.5 in responders, versus 17.3 ± 7.6 in nonresponders. The acitretin median daily dose was 0.44 ± 0.13 mg/kg in responders and 0.38 ± 0.14 mg/kg in nonresponders (Table 2).

TABLE 1. Overview of Clinical Characteristics, Treatment Course and Outcome of 18 Children and Adolescents with Plaque Psoriasis Treated with Acitretin

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>12 (66.6)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>6 (33.3)</td>
</tr>
<tr>
<td>Age at start of acitretin, years, range (median)</td>
<td>2–14 (9.5)</td>
</tr>
<tr>
<td>Daily dose at start of acitretin, mg/kg</td>
<td>0.2–0.5</td>
</tr>
<tr>
<td>Daily maintenance dose, mg/kg, median ± SD</td>
<td>0.41 ± 0.14</td>
</tr>
<tr>
<td>Responders, n (%)</td>
<td>8 (44.4)</td>
</tr>
<tr>
<td>Total treatment duration in responders, months, mean ± SD</td>
<td>22.7 ± 12.0</td>
</tr>
</tbody>
</table>

TABLE 2. Comparison of Responders and Nonresponders

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Responders, (n = 8)</th>
<th>Nonresponders, (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Female, n</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Age at start of acitretin, years, mean ± SD</td>
<td>9.6 ± 3.3</td>
<td>9.2 ± 4.1</td>
</tr>
<tr>
<td>Previous systemic treatments, n</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Baseline Psoriasis Area and Severity Index score, mean ± SD</td>
<td>17.5 ± 8.5</td>
<td>17.3 ± 7.6</td>
</tr>
<tr>
<td>Maintenance acitretin dose, mg/kg/day, mean ± SD</td>
<td>0.44 ± 0.13</td>
<td>0.38 ± 0.14</td>
</tr>
</tbody>
</table>
Acitretin was effective in 44.4% of patients, although because of the lack of a control group, it is not possible to know how much of the improvement was due to the drug as opposed to spontaneous improvement or remission. Discontinuation of treatment was associated with relapses, but re-treatment was effective.

Pediatric and adolescent psoriasis can have a profound effect on the psychological health of patients and their families. Affected subjects are more likely to experience anxiety, depression, lack of sexual intimacy, joint pain, chronic itching, and lack of social connectivity (8–10) and to develop psychiatric disorders (11).

Treatment of moderate to severe psoriasis in childhood is often challenging. The Food and Drug Administration has not approved any of the available treatments of moderate to severe plaque psoriasis in adults (phototherapy, methotrexate, cyclosporine, retinoids, biologic agents) for use in children. Conversely, the European Medicines Agency approved etanercept and more recently adalimumab and ustekinumab. In particular, etanercept is licensed for the treatment of chronic severe plaque psoriasis in children ages 6 years and older who are inadequately controlled by or are intolerant to other systemic therapies or phototherapies. The European Commission has approved adalimumab for the treatment of severe chronic plaque psoriasis in children and adolescents ages 4 years and older who have had inadequate response to or are inappropriate candidates for topical therapy and phototherapy. Ustekinumab has been approved for the treatment of moderate to severe plaque psoriasis in adolescents ages 12 years and older who are inadequately controlled by or are intolerant to other systemic therapies and phototherapy.

According to expert consensus, systemic therapeutic agents should be considered in cases of inadequate response or contraindications to topical or UV light and in extensive and chronic cases (12), although studies in children are insufficiently documented with regard to drug dosing regimens, efficacy, and safety. Physicians rely on long-term experience of these drugs for adults or for other pediatric diseases (10). Doses for children are often designed by scaling from adult dosages after adjusting for body weight.

Acitretin is the free and active metabolite of etretinate, the first oral synthetic retinoid used in the treatment of psoriasis and other disorders of keratinization. It is the only nonimmunosuppressive agent of the antipsoriatic systemic drugs. Its mechanism of action remains unknown. Retinoids primarily act by normalizing keratinocyte differentiation, decreasing epidermal proliferation; they also exert immunomodulatory and antiinflammatory effects without direct immunosuppressive action (13,14). Effects on epidermal cell growth and differentiation may be responsible for their therapeutic action in psoriasis (15). Treatment of psoriatic skin with acitretin results in a reduction of the proliferation rate in acanthotic epidermis, promotion of terminal differentiation of keratinocytes, regulation of desquamation of corneocytes, and a decrease of the thickness of the stratum corneum and inflammation in the epidermis and dermis (5). Consequently, this antiproliferative effect decreases desquamation, erythema, and the overall thickness of the psoriatic lesion (16). As monotherapy, acitretin is considered to be more effective in pustular and erythrodermic psoriasis than in chronic plaque-type psoriasis (17,18). Mucocutaneous side effects such as cheilitis, xerosis, epistaxis, skin fragility, hair loss, and ocular toxicities occur in almost all patients to varying degrees and may limit therapy in adults and children (11,19). Dose-proportional retinoid-associated hyperlipidemia has been observed in 25% to 40% of patients (20).

Acitretin is a pregnancy category X drug and is contraindicated in women of childbearing age. Women of childbearing potential must use reliable contraception during treatment and for at least 3 years after cessation of therapy. Its safety and effectiveness in children have not been established.

Discussion

Our study represents the largest case series of children treated with acitretin for plaque psoriasis to date. Acitretin was effective in 44.4% of patients, although because of the lack of a control group, it is not possible to know how much of the improvement was due to the drug as opposed to spontaneous improvement or remission. Discontinuation of treatment was associated with relapses, but re-treatment was effective.

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because clinical trials have not been conducted in children. Some clinical experience derives from other clinically relevant subsets, such as keratinization disorders (21), that require long-term treatments. Ossification of interosseous ligaments and tendons of the extremities, skeletal hyperostoses, decreases in bone mineral density, and premature epiphyseal closure have been reported after prolonged use of etretinate but not acitretin (16,22). British Association of Dermatologist guidelines do not recommend acitretin in children (21). De Yager et al (6) and Van Geel et al (7) concluded that the efficacy and safety of retinoids is mainly documented in pustular and erythrodermic pediatric psoriasis, whereas studies in childhood plaque psoriasis are lacking. As a result, therapeutic algorithms (6,7) propose methotrexate as the systemic therapy of choice of childhood psoriasis, suggesting acitretin be considered only in pustular and erythrodermic psoriasis. Acitretin was administered in 11.2% of children attending a tertiary referral psoriasis clinic (23).

In our group of pediatric patients, the overall response rate to acitretin was comparable with that in adults (24,25). Acitretin was administered as the first systemic therapy in 72.2% of patients. A presumed better safety profile of acitretin with respect to the majority of immunosuppressant therapeutic options may explain this choice. Adverse events registered during clinical follow-up were generally mild. Mucocutaneous adverse effects occurred in all patients, but they did not affect therapy maintenance. Only one patient discontinued treatment because of arthralgia, which required a different therapeutic approach. Laboratory anomalies, in particular hepatic function and dyslipidemia, did not emerge as relevant during treatment, confirming that tolerability with respect to lipid metabolism and hepatic function is usually good in children (12). It is possible that, at equivalent doses, children are less likely to have retinoid-induced systemic side effects. In addition, acitretin dosage did not exceed 0.6 mg/kg/day. The incidence of acitretin-associated clinical and laboratory adverse events has been shown to be largely dose dependent (16,17,25,26). Specific monitoring of bone parameters was not undertaken in this study.

Several limitations need to be considered. Selection bias was possible because the data were gleaned from existing records. Although contributing centers were asked to report all cases of childhood psoriasis treated with acitretin, we cannot completely exclude the possibility of reporting bias. Information bias cannot be excluded, with a possible optimistic picture of the results in terms of the description of effectiveness and safety, because only side effects that appeared during clinical follow-up were included. The study lacked a predefined study protocol. Because of the multicenter setting, dosages and scheduled courses of treatment were not standardized. Effects on bone were not formally investigated. Despite these possible limitations, we think that our findings may be of interest in expanding our knowledge, attitudes, and practices regarding acitretin in recalcitrant childhood psoriasis.

CONCLUSIONS

Acitretin may be moderately effective in children with moderate to severe plaque psoriasis. Given the small number of patients, statements about long-term safety are not possible. Because of the need for prolonged, usually lifelong, treatment also in children with psoriasis, health systems should support the design of disease or patient registries. Extensive databases may be useful for recording prospective data on efficacy, safety profiles, and suitable dosages of available therapies for childhood psoriasis.

FINANCIAL DISCLOSURE

V. Di Lernia served as Advisory Board Member for AbbVie. C. Lasagni received honoraria from Abbott, Pfizer, and Janssen. P. Gisondi has been a consultant or speaker for Abbott, Janssen, Leo-Pharma, Lilly, Merck Sharp & Dohme, Novartis, and Pfizer.

REFERENCES