Low-Dose Acitretin Is Associated With Fewer Adverse Events Than High-Dose Acitretin in the Treatment of Psoriasis

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Objective: In practice, lower dose acitretin therapy (25 mg/d) seems to be better tolerated and associated with fewer abnormalities found after laboratory testing. Here we revisit the original phase 3 trials for acitretin to evaluate the evidence for low-dose therapy producing fewer adverse effects than the 50 mg/d dosage.

Design: We retrospectively analyzed pooled data from 2 large pivotal trials, each including a randomized, placebo-controlled, 8-week double-blind phase followed by a 16-week open-label phase.

Setting: Multicenter pivotal trial of subjects in referral centers and private practice.

Participants: Subjects with severe psoriasis requiring systemic therapy were recruited according to inclusion/exclusion criteria.

Intervention: During the double-blind phase, subjects received placebo or one of several fixed acitretin doses. Dose adjustment was allowed during the open-label phase, during which high-dose treatment was defined as a mean dosage of 50 mg/d and low-dose treatment was defined as a mean dosage of 25 mg/d.

Main Outcome Measures: The frequency of anomalies found after laboratory testing and clinical adverse events were the outcomes of interest.

Results: Common adverse effects (dry skin, alopecia, rhinitis, etc) were 2 to 3 times more frequent in subjects receiving 50-mg/d acitretin than in those receiving 25 mg/d. Increases in hepatic enzymes and triglycerides in subjects receiving low-dose therapy were minimal compared with levels in those receiving high-dose therapy.

Conclusions: We have shown low-dose therapy (25 mg/d) to be an effective strategy for substantially reducing acitretin-associated adverse effects. Many adverse effects associated with acitretin therapy are dose dependent and can limit the usefulness of this potentially beneficial therapy.

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Acitretin occupies a unique position within the psoriasis therapeutic armamentarium. It is currently the only oral retinoid approved for psoriasis and can be effective in treating refractory and severe variants such as erythrodermic, pustular, and palmoplantar forms. Acitretin is particularly effective when used in combination with phototherapy for moderate-to-severe plaque-type psoriasis. Although skeletal hyperostosis is seen infrequently with long-term use of high-dose acitretin and although acitretin is teratogenic, this agent has the advantage of none of the cumulative toxicities seen with traditional systemic psoriasis treatments.

The effectiveness and safety of acitretin for treatment of psoriasis were evaluated more than a decade ago in 2 pivotal trials (Connetics Corporation, data on file, 1996). Results from these trials showed 50-mg/d acitretin to have superior effectiveness compared with placebo and with lower doses after 8 weeks of treatment. On the basis of these data, acitretin subsequently received US Food and Drug Administration approval for use at dosages of 25 to 50 mg/d.

However, at the 50 mg/d dosage, acitretin exhibits a relatively high rate of adverse events, a finding in the original pivotal trials as well as in subsequent clinical practice (also D.J.P.; Kristen B. Higgins, MD; Katherine Stealey, MD; Rajesh Balkrishman, PhD; Martha Crane, PhD; Fabian Camacho, MD; Alan Fleischer, MD; S.R.F.; unpublished data, 2006). Most are minor and include dry skin and mucous
membranes, pruritus, alopecia, rhinitis, epistaxis, nail disorder, and swollen or bleeding gums. Gastric symptoms also have been reported and include stomach pain, diarrhea, and vomiting. Nonspecific headaches, hot flashes, and flushing also may occur. Other serious but rare adverse effects include blurred vision, eye pain, photosensitivity, swelling of extremities, depression, suicidal ideation, bone and muscle pain, numbness and tingling in hands or feet, chest pain, confusion, arrhythmias, dizziness, and shortness of breath. As a systemic retinoid, acitretin is metabolized by the liver and has the potential to perturb hepatic function. Another known adverse effect of acitretin in some individuals is the potential to elevate serum triglycerides (TGs) to significant levels; routine monitoring is advised (also K.K.Z., E.J.M., D.J.P., R.R., and S.R.F., unpublished data, 2005). Despite this adverse effect profile, acitretin features prominently in many monotherapy and combination regimens.

We have revisited the original acitretin pivotal trials to determine the ability of low-dose treatment to reduce the frequency of adverse events while effectively treating psoriasis. Although the results from the acitretin pivotal trials showed the 50 mg/d dosage to be more effective than the 25 mg/dosage after 8 weeks of treatment, subsequent experience has suggested that longer treatment is necessary to observe full therapeutic effects of oral retinoids, especially at low doses. Results of an analysis of acitretin pivotal trial data showed the 25 mg/d dosage to provide effectiveness equal to or better than the 50 mg/d dosage across 24 weeks of treatment. The present article represents a parallel effort: we retrospectively analyzed pooled data from the 2 acitretin pivotal trials to determine whether the 25 mg/dosage can reduce adverse events substantially, including abnormal laboratory test results, such as TG and hepatic enzyme levels, to significant levels; routine monitoring is advised (also K.K.Z., E.J.M., D.J.P., R.R., and S.R.F., unpublished data, 2005). Despite this adverse effect profile, acitretin features prominently in many monotherapy and combination regimens.

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**METHODS**

We analyzed pooled adverse event data from both double-blind (DB), placebo-controlled acitretin pivotal trials and their open-label (OL) extensions. These trials generated effectiveness and safety data to support the original acitretin new drug application; our reanalysis of the effectiveness data from these trials is discussed in a separate report along with a more detailed description of methods. Two categories of adverse events are analyzed here: laboratory events and clinical events.

**SUBJECTS**

In both trials, adult subjects with extensive or disabling psoriasis were enrolled. Subjects were excluded if they were of child-bearing potential or were nursing a child. Subjects also were excluded if they had previously received retinoid treatment, had any condition that could be exacerbated by hypervitaminosis A, had preexisting hyperlipidemia, or had impaired renal function. The use of any other therapy intended for treatment of psoriasis, including oral or topical medication or ultraviolet light, was not allowed.

**TRIAL DESIGN**

In trial A (n=171), 2 dosages of acitretin (25 and 50 mg/d) were compared with placebo, whereas in trial B (n=333) 4 dosages of acitretin (10, 25, 50 and 75 mg/d) were compared with placebo. Both trials consisted of 2 phases: 8 weeks of placebo-controlled, DB treatment immediately followed by 16 weeks of OL use. At the outset of the DB phase, subjects were assigned randomly to a fixed dose by means of a computer-generated code. During the 16-week OL phase, dose increases or reductions were allowed to optimize effectiveness and tolerability for each subject. Subjects receiving placebo during the DB phase were allowed to begin treatment with acitretin, also at individually tailored doses, during the OL phase.

**END POINTS**

Clinical adverse events were monitored throughout the study. During the DB phase, laboratory tests were conducted at baseline and at the end of weeks 1, 2, 4, 6, and 8. During the OL phase, laboratory tests were conducted at weeks 12, 16, 20, and 24. Laboratory tests to evaluate lipid metabolism and hepatic function included total cholesterol, high-density lipoprotein, TGs, bilirubin, lactate dehydrogenase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and total protein.

**STATISTICAL ANALYSIS**

For purposes of data analysis, during the DB phase low-dose acitretin was defined as 25 mg/d and high-dose acitretin was defined as 50 mg/d. Because doses were titrated up or down as needed during the OL phase, low- and high-dose treatment groups were defined on the basis of mean daily dose, with average dosages of 30 mg/d or lower defined as low dose and average dosages higher than 30 mg/d defined as high dose. As reported elsewhere, these definitions yielded group-wide average dosages of 22.2 to 24.4 mg/d for the low-dose groups and 50.0 to 52.4 mg/d for the high-dose groups during the OL phase.

By using these definitions of low- and high-dose treatment, the data from trials A and B were combined, and 2 separate analyses were performed on the pooled subject population data. In analysis 1, subjects were categorized into 4 groups according to the dose received during the DB phase and the OL phase: high-dose DB to low-dose OL (H to L, n=23), high-dose DB to high-dose OL (H to H, n=77), low-dose DB to low-dose OL (L to L, n=19), and low-dose DB to high-dose OL (L to H, n=32). To examine the effect of dose on clinical adverse event rates, we examined only the L-to-L and H-to-L groups in this article.

In analysis 2, subjects were grouped according to the dose of acitretin received during the 8-week DB phase only, regardless of the dose eventually used during the OL extension. There were 3 different dosing groups in the DB phase: placebo (n=101), 10 mg/d (n=26), 25 mg/d (n=75), 50 mg/d (n=101), and 75 mg/d (n=28). Of these groups, placebo, 25 mg/d, and 50 mg/d are included in the present analysis. All analyses were conducted in an intent-to-treat analysis.

For analyzing adverse events, the treatment period was considered to extend 3 days beyond the end of therapy because this 3-day window parallels the half-life of acitretin elimination: 49 hours for acitretin (range, 33-96 hours) and 63 hours for the metabolite cis-acitretin (range, 28-157 hours); note that acitretin metabolite half-lives as long as 168 days are seen with concomitant ethanol intake (K.K.Z., E.J.M., D.J.P., R.R., and S.R.F., unpublished data, 2005). Therefore, subjects were evaluated for adverse events 3 days after taking their last acitretin dose.
RESULTS

CLINICAL EVENTS

Analysis 1

The global clinical adverse event rate was 94% during the DB phase and 78% during the OL phase. Roughly 1 in 4 subjects received a low (25 mg) daily dose during the OL phase, regardless of the dose received during the DB phase (27% of subjects received 25 mg, and 23% of subjects received 50 mg). Among all subjects in the L-to-L and H-to-L groups, the 5 most common adverse effects were the same during both phases of the study: cheilitis, skin peeling, pruritus, alopecia, and rhinitis. There was a statistically significant reduction in the overall adverse event rate for the H-to-L group; 100% during the DB phase to 82% during the OL phase (P = .04). For the L-to-L cohort, the adverse event rate also decreased, although not as far, from 87% to 74%. A summary of the 10 most reported adverse events is given in Figure 1: the frequencies for each of these are given for both groups and at 8 and 24 weeks. In the H-to-L group, there was a reduction in the occurrence of all 10 adverse events after switching from high-dose therapy (DB phase) to low-dose therapy (OL phase).

Analysis 2

During the DB period, adverse events were significantly greater in both the 25-mg and 50-mg groups when compared with placebo. Subjects taking 50 mg/d of acitretin had adverse events at a higher frequency than did subjects taking 25 mg/d (Figure 2). During the first 8 weeks of treatment, the most common adverse effects were cheilitis, skin peeling, rhinitis, pruritus, dry skin, alopecia, xerophthalmia, rash, paresthesia, nail disorder, and skin atrophy. In analysis 2, all adverse events were dose dependent except for pruritus, which occurred more frequently in the 25-mg group (Figure 2); this apparent lack of dose dependency for pruritus was not seen in analysis 1. Attrition was higher, although not significantly, in the 50-mg group, in which 4 subjects discontinued therapy compared with only 1 subject who received 25 mg/d (P = .40).

LABORATORY EVENTS

Lipid Metabolism (Analyses 1 and 2)

There were no consistent trends in total cholesterol values between time points or between dosing groups. Baseline cholesterol levels were similar, with a mean of 228.38 mg/dL (5.92 mmol/L) across all 4 dose groups. At the end of the DB phase, mean percentage increases for each of the 4 dosing groups ranged from 1.82% to 2.92% over baseline. At the end of the OL phase, the mean percentage change from baseline ranged from −1.74% to 7.31% (seen in the H-to-L and L-to-H groups, respectively). High-density lipoprotein values decreased in all 4 cohorts after the DB and OL phases, although these decreases did not exhibit any specific trends with respect to the dose received. After 8 and 24 weeks of therapy, the mean reductions in high-density lipoprotein across all 4 groups were 6.54% and 5.26%, respectively. By the end of 8 weeks, mean lactate dehydrogenase values had increased for all cohorts except for 1 of the 2 groups receiving low-dose therapy (L-to-H group). By the end of 24 weeks, all 4 cohorts exhibited increased mean values for lactate dehydrogenase, although these changes did not appear to be dose dependent.

Triglyceride levels were elevated in all 4 cohorts at the end of the DB and OL phases, and the degree of increase roughly correlated with the acitretin dose most recently received. At the end of the DB phase, TG increases were roughly twice as large for the 2 high-dose groups (H to H and H to L) as for the 2 low-dose groups (L to L and L to H). By the end of the OL phase of the study, the groups with the smallest percentage increase in TG levels were the L-to-L and H-to-L groups, which had received low-dose acitretin for the past 24 and 16 weeks, respectively. Comparing cohorts that received low-dose therapy vs high-dose therapy for 24 weeks shows that the increases in TG levels were +1.3% and 54.5%, respectively, representing an absolute difference of 13.2% (Table).

Hepatic Function (Analyses 1 and 2)

Throughout the DB and OL phases, there was no obvious pattern of increase or decrease in total bilirubin, pro-
tein, or alkaline phosphatase. Although there were minor fluctuations, no trends were noted. Mean liver enzyme levels (ALT and AST) increased while subjects were receiving acitretin, and these mean increases were strongly dose dependent. By the end of the 8-week DB phase, subjects receiving high-dose acitretin (H-to-H and H-to-L groups) had substantially higher mean increases in both ALT and AST than did subjects receiving the 25 mg/d dosage (L-to-L and L-to-H groups). By the end of 24 weeks, all 3 groups that had received high-dose treatment in either the DB or the OL phase (L-to-H, H-to-L, and H-to-H groups) exhibited higher mean increases in both ALT and AST than did the L-to-L group, which received low-dose treatment throughout the entire trial (Table).

Adverse events are common during acitretin therapy. These events are rarely life-threatening, although they may affect therapy. Negative experiences in clinical practice may limit the use of an agent, and high adverse event rates may compromise treatment success. In this analysis, we demonstrated that the incidence of acitretin-associated clinical and laboratory adverse events is largely dose dependent; many of these events may be avoided by using acitretin dosages of 25 mg/d. It is reasonable to speculate that by reducing adverse events and therefore the risk of discontinuation, low-dose acitretin may, in practice, result in better long-term effectiveness compared with results with higher doses. From this analysis, we conclude that adverse events are less frequent after acitretin dose reduction.

Consistent with this hypothesis, results of a separate analysis indicated that 25 mg/d of acitretin provided levels of effectiveness across 24 weeks that were at least as high as those seen with 50 mg/d of acitretin across the same treatment period (K.K.Z., E.J.M., D.J.P., R.R., and S.R.F., unpublished data, 2005). The relevance of this effect cannot be understated in psoriasis therapy, where there are a limited number of treatments and all are linked to adverse events. Psoriasis is a chronic disease in which many patients require long-term therapy. To date, providing sustainable treatment has presented a challenge because of significant adverse events and poor compliance.

Although the data analyzed here were collected through a prospective, placebo-controlled, randomized trial, the retrospective nature of this article represents an obvious limitation. In addition, the clinical adverse events considered here are often symptoms, and therefore not easily validated, because it may be difficult to determine objectively the extent to which each patient is affected. A thorough effort should be made to screen for clinical adverse events in patients receiving acitretin. In addition to being dose related, many of the minor events noted in this analysis may be relieved with moisturizers. Dry eyes, or xerophthalmia, for example, occurred in 4% to 18% of subjects, according to the dose received in the study, and often is remedied easily with drops.
Significant abnormalities found after laboratory testing are uncommon with acitretin use and appear to be even less common with low-dose therapy. Indicators of hepatic dysfunction directly correlated with high-dose therapy; large mean increases in ALT and AST were seen in all groups receiving high-dose acitretin (L-to-H, H-to-L, and H-to-H). However, median increases in these enzymes were not nearly as large; in the L-to-H group, for example, mean ALT increase was 52.0% by the end of the OL phase, compared with a median increase of 0%. Taken together, these observations suggest that most patients have mild if any elevations in these enzymes and that extreme elevations, which contributed to the observed mean increases in enzyme levels, are relatively rare.

Because of its teratogenic effects, acitretin should not be used at any dose as first-line therapy for women of childbearing potential, unless other therapies are contraindicated or ineffective. If acitretin is used in such women, 2 forms of reliable contraception must be used, and pregnancy must be avoided during treatment and for at least 3 years after cessation of treatment. The potential for skeletal abnormalities with acitretin also must be considered, although this phenomenon is seen primarily in long-term, high-dose treatment and is uncommon.

Overall, the results of this and other concurrent retrospective analyses of acitretin pivotal trial data strongly support the effectiveness of low-dose (25 mg/d) acitretin for use in some patients with psoriasis as a means of reducing the risk of common clinical and laboratory adverse events without sacrificing long-term effectiveness.

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