Efficacy and Cutaneous Safety of Adapalene in Black Patients Versus White Patients With Acne Vulgaris

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Acne vulgaris is the most common dermatologic disorder seen in American black patients (ie, African Americans and African Caribbeans, Fitzgerald skin types IV through VI). Despite its prevalence, there is a lack of data on the effects of treatments, such as the use of topical retinoids and retinoid analogs, in this patient population. Adapalene is a topical retinoid analog that has demonstrated efficacy in the reduction of noninflammatory and inflammatory lesions, along with excellent cutaneous tolerability. Most clinical studies of this agent have involved predominantly white patient populations. This meta-analysis of 5 randomized US and European studies was designed to evaluate the efficacy and safety of adapalene in black versus white patients. The percentage reduction in the number of inflammatory lesions was significantly greater among black patients compared with white patients (P=.012). The percentage reductions in total inflammatory and noninflammatory lesion counts were similar in the 2 groups (P>.3). There were significantly less erythema and scaling in black patients compared with white patients (P<.001 and P=.026 for worst scores for erythema and scaling, respectively). Although the incidence of dryness was similar in both groups, a smaller percentage of black than white patients had moderate or severe scores for dryness (7% vs 18%, respectively). In summary, adapalene appears to be a viable treatment for black patients with acne vulgaris.

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Numerous well-controlled clinical trials have confirmed the efficacy and safety of various formulations of adapalene, a topical retinoid analog, for the treatment of both the inflammatory and noninflammatory lesions of acne vulgaris.[1-7] In these core clinical trials, as well as in studies designed to evaluate cutaneous safety as a primary end point,[8-10] adapalene consistently has demonstrated the best tolerability profile of all the topical retinoids and retinoid analogs used. Patients with white skin (Fitzgerald skin types I through III) predominantly comprised the study populations in these clinical trials, as well as in those clinical trials evaluating other topical retinoids and retinoid analogs.

A survey performed almost 2 decades ago by Halder and colleagues[11] and a more recent one by Taylor and colleagues[12] revealed that acne vulgaris is the most common dermatologic condition in African Americans yet is less well characterized in Africans, African Americans, and African Caribbeans (Fitzgerald skin types IV through VI). Furthermore, there is a paucity of clinical studies specifically evaluating the effects of therapeutic interventions, such as topical retinoids (eg, tretinoin) or retinoid analogs (eg, adapalene, tazarotene), in this patient population.

Recent studies have suggested that the pathogenesis of acne vulgaris in people with skin of color is probably similar to that in people with lighter skin color.[12] Indeed, Halder et al[11] reported the potential histologic differences between the acne vulgaris lesions in African Americans and those in whites. The researchers took biopsy specimens of facial comedones and of papular and pustular lesions from 30 African American females. Notably, marked inflammation with infiltrates of polymorphonuclear leukocytes was observed in the

comedones, conventionally classified as noninflammatory, as well as in the classic inflammatory lesions.[13]

Increasingly, the pathophysiological role of inflammation in all acne vulgaris lesions is being recognized.[14,15] The presence of inflammatory infiltrate in acne lesions in people with skin of color is especially noteworthy because of the propensity for this population to develop postinflammatory hyperpigmentation or hyperpigmented macules.[12,16]

Few studies have evaluated the effects of topical retinoids or retinoid analogs on acne lesions in people with skin of color. A recent double-blind, vehicle-controlled study on topical tretinoin 0.025% cream in 27 black patients with acne vulgaris found that this treatment resulted in a significant decrease in papules, pustules, and hyperpigmented macules. However, irritation and inflammation were problematic side effects experienced by many of the patients in the study.[17] A recent open-label study[18] of adapalene gel 0.1% in African patients with acne vulgaris demonstrated significant improvement in inflammatory and noninflammatory lesions and hyperpigmentation disorders. In contrast to studies with other topical retinoids, fewer than 5% of patients treated with adapalene gel 0.1% reported moderate or severe skin irritation during the study.[18]

The following meta-analysis evaluated the use of adapalene 0.1% gel in black patients and compared the results with those in white patients.

Methods

The objective of this meta-analysis was to compare results from previous clinical trials, specifically the efficacy and safety of adapalene gel 0.1% in black versus white (mostly of European ancestry) patients with acne vulgaris. Data from a previous meta-analysis were analyzed in this study, using only those related to subpopulations of black patients and white patients from the 5 randomized clinical trials performed in the United States or Europe[7]; the total number of black patients treated with adapalene in all of these trials combined was small (Table 1). The studies could be of any duration, but only subjects treated with adapalene were included in this analysis. Subjects randomized to other treatment arms (vehicle or active comparator) were excluded.

A total of 655 patients were included in the analysis: 46 black patients and 609 white patients (Table 1). Baseline lesion counts were similar between both groups. An intent-to-treat patient population (ie, all patients enrolled and randomized to the adapalene treatment arm) was used in the efficacy and safety analysis.

The primary efficacy parameters evaluated were total lesion counts (sum of inflammatory and noninflammatory lesions), inflammatory lesion counts, and noninflammatory lesion counts. An efficacy end-point value was calculated using the last observation recorded on each patient, then carried forward up to week 12 of treatment. Statistical analysis

Table 1.

Numbers of Black Patients and White Patients Evaluated in Meta-analysis Among 5 Studies

	Patient Subpopulations			
	Black		White	
Study	n	%	n	%
1	19	11.7	143	88.3
2	6	8.3	66	91.7
3	5	3.9	124	96.1
4	14	6.9	190	93.1
5	2	2.3	86	97.7
All	46	7.0	609	93.0

Table 2.

Efficacy Results of Meta-analysis: Percentage Reduction in Inflammatory, Noninflammatory, and Total Lesions in Black Patients Versus White Patients*

			Patient Subpopulations			
			Black (n=46)		White (n=609)	
Parameter	Visit	Type	LS Mean	SE	LS Mean	SE
Inflammatory lesions	Baseline	Count	21.14	2.21	23.32	0.64
	End point	Count	9.28	2.04	14.89	0.59
		Reduction, %	53.29†	6.65	36.12	1.92
Noninflammatory lesions	Baseline	Count	62.17	6.48	59.12	1.87
	End point	Count	34.78	6.38	36.51	1.84
		Reduction, %	44.13	5.90	41.81	1.70
Total lesions	Baseline	Count	83.31	7.03	82.44	2.02
	End point	Count	44.06	7.19	51.40	2.07
		Reduction, %	45.76	5.05	41.07	1.45

*LS indicates least square.
†P=.012 for reduction in inflammatory lesions in black vs white patients.

between both groups was done for the percentage reduction in lesion counts at week 12 from baseline.

The primary safety parameters evaluated were erythema, scaling, and dryness. Each of these adverse events was evaluated on a 0 to 3 point scale: 0=none, 1=mild, 2=moderate, and 3=severe. A worst score (maximum score or the most severe degree of adverse event observed over all postbaseline visits) was calculated for the safety evaluation.

Statistical Analysis—The ratio of black to white patients was not uniform across trials used in this meta-analysis. Therefore, in addition to unadjusted estimates obtained by pooling the results by race across trials, adjusted estimates also were calculated. For lesion count and percentage reduction from baseline in lesion count, an analysis of variance was performed for baseline and end point only. The model included effects for study and race (black and white). Least squares methods were estimated for each type of lesion by race. These estimates were adjusted for natural study-to-study variations.

The Cochran-Mantel-Haenszel test, stratified by study using the Ridit transformation, was used to compare the percentage reduction from baseline in lesion counts (total, noninflammatory, and inflammatory) and the cutaneous safety parameters in black versus white patients. This statistical analysis was equivalent to a stratified Mann-Whitney (nonparametric) test.

Results

Efficacy—Combined efficacy results for all analyzed studies are summarized in Table 2. There were no significant differences in total numbers of baseline lesions or in end-point lesions between groups. Also, there were no significant differences in noninflammatory lesions between groups at both time points. Similarly, the percentage reductions in both total and noninflammatory lesions with adapalene gel 0.1% in black versus white patients were not significantly different (P>.3). However, while baseline inflammatory lesion counts were similar for both black and white patients (21.14 and 23.32, respectively), the percentage reduction in inflammatory lesion counts was significantly greater in black patients than in white patients (P=.012)(Figure 1).

Safety—Combined tolerability results for dryness, erythema, and scaling are shown in Table 3. Although the incidence of either mild or no dryness was similar in both groups, a smaller percentage of black than white patients had a moderate or severe score for dryness (7% vs 18%, respectively)(Table 3). Overall, there was significantly less erythema and scaling in black patients than

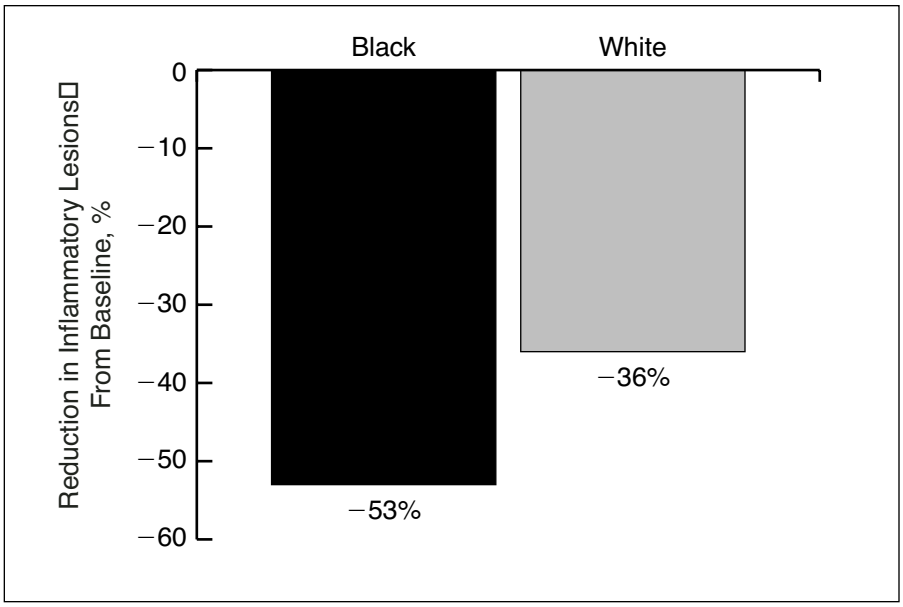

Figure 1. Percentage reduction in inflammatory lesions with adapalene gel 0.1% was significantly greater in black vs white patients (P=.012).

Table 3.

Cutaneous Tolerability Results of Meta-analysis: Distribution of Worst Scores in Black Patients Versus White Patients

		None		Mild		Moderate		Severe	
Parameter	Patient Subpopulations	n	%	n	%	n	%	n	%
Dryness	Black	15	34.1	26	59.1	2	4.55	1	2.27
	White	181	30.2	310	51.7	104	17.3	5	0.83
Erythema	Black*	34	77.3	9	20.5	1	2.27		
	White	198	33.0	300	50.0	98	16.3	4	0.67
Scaling	Black†	24	54.5	19	43.2	1	2.27		
	White	244	40.7	266	44.3	82	13.7	8	1.33

*P<.001 for combined worst scores for erythema in black vs white patients.
†P=.026 for combined worst scores for scaling in black vs white patients.

in white patients (P<.001 and P=.026 for combined worst scores for erythema and scaling, respectively). When the distribution of worst scores was analyzed, the percentage of black patients with worst scores of none clearly drove the better tolerability regarding erythema in that group (Figure 2). Similar distributions of worst scores for scaling were seen between the 2 patient subpopulations (Figure 3). Overall worst scores demonstrated significantly better results for scaling in black patients.

Comment

Numerous clinical trials have demonstrated the efficacy of adapalene for reducing inflammatory and noninflammatory lesions in white patients. Therefore, this study was not designed to provide a statistical analysis of the effect of this topical retinoid analog in the general population used in this meta-analysis, the majority of whom were white. Rather, the objective of this trial was to assess how efficacy and safety results for adapalene in black patients compared with those in white

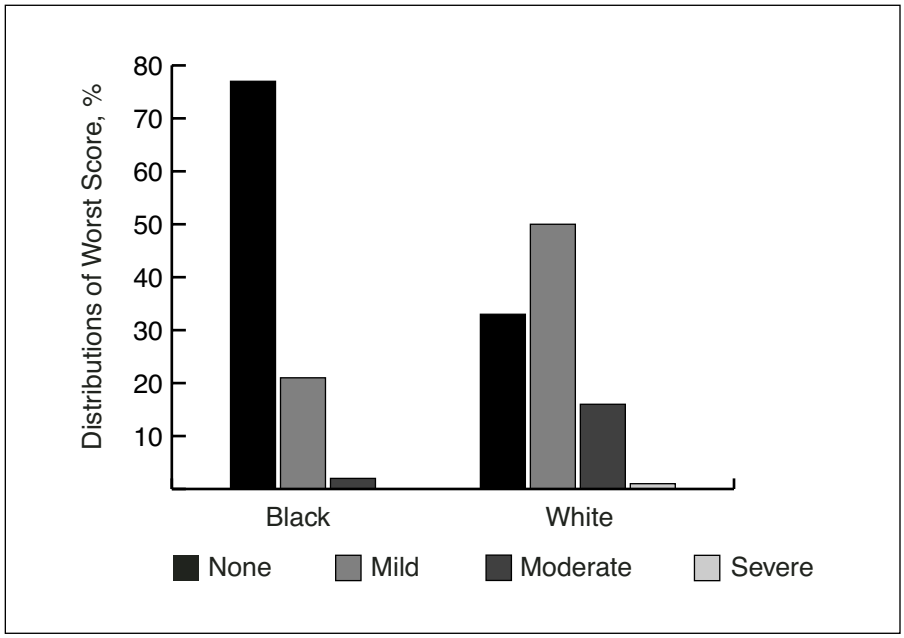

Figure 2. Distribution of worst scores for none, mild, moderate, and severe erythema in black vs white patients ($P<.001$).

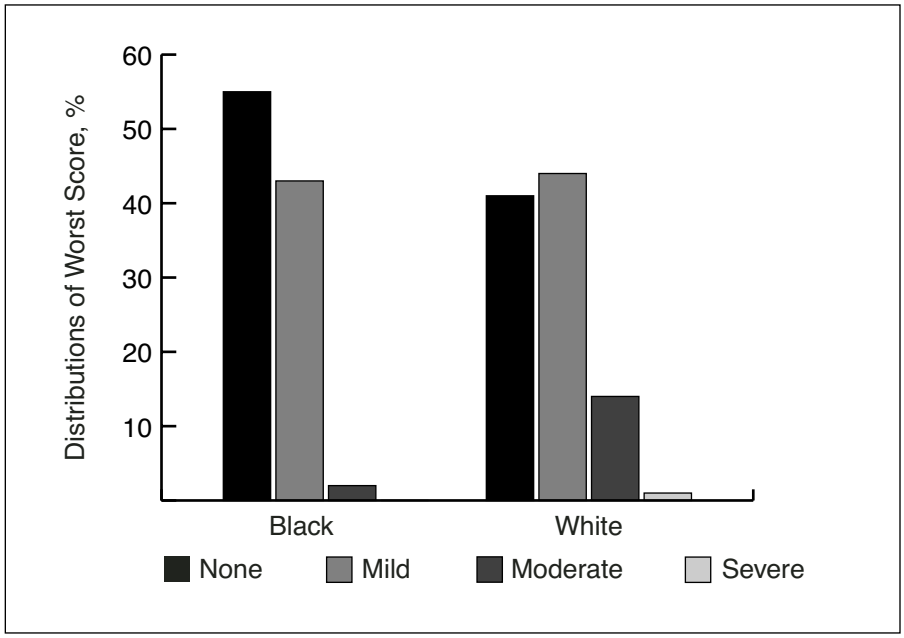

Figure 3. Distribution of worst scores for none, mild, moderate, and severe scaling in black vs white patients ($P=.026$).

patients. One interesting finding was the greater reduction in inflammatory lesions in black compared with white patients (Table 2)(Figure 1). Adapalene has demonstrated significant anti-inflammatory and immunomodulating effects in preclinical trials[19,20] and significant reduction in inflammatory lesions in other clinical trials.[1-7] Why adapalene demonstrated a greater effect on inflammatory lesions in black patients is not known. It has been speculated that black patients with inflammatory lesions may exhibit marked inflammation.[12] Black patients with such marked inflammatory infiltrates may respond especially well to the anti-inflammatory effects of adapalene.

The small sample size of black patients used in this meta-analysis is a limitation of this study. However, in addition to using unadjusted estimates (pooling the results by race across trials), the use of adjusted estimates also was calculated to account for the small number of black patients across trials. Nevertheless, definite conclusions regarding any specific response of black patients to the anti-

inflammatory effects of adapalene cannot be drawn at this time.

The black patients in this meta-analysis also exhibited greater tolerability to adapalene compared with white patients. Black patients experienced significantly less erythema and scaling (Figures 2 and 3) and a trend toward a lower incidence of moderate to severe dryness (Table 3). Although erythema is often underestimated in people with skin of color because of the masking effects of melanin,[16] no such underestimation has been reported for other cutaneous adverse events, such as dryness and scaling. Minimizing cutaneous irritation while effectively treating inflammatory and noninflammatory lesions is especially critical in black patients with acne vulgaris to help avoid inflammatory reactions that could lead to postinflammatory hyperpigmentation.[16]

Conclusion

The objective of this meta-analysis was to evaluate the efficacy and safety of adapalene in the treatment of both inflammatory and noninflammatory lesions in black patients compared with white patients across several different studies. In black patients, adapalene demonstrated significantly greater efficacy in the reduction of inflammatory lesions and significantly greater cutaneous tolerability, as evidenced by a decreased incidence of erythema and scaling. Based on the results of this study and a previous study[18] on the use of adapalene in African patients with acne vulgaris, adapalene appears to be a viable treatment for acne vulgaris in patients with skin of color.

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