Comparative Efficacy and Tolerability of Dapsone 5% Gel in Adult Versus Adolescent Females with Acne Vulgaris

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ABSTRACT

Objective: To determine whether the response to dapsone 5% gel was similar in adolescent girls and adult women with facial acne vulgaris. **Design and setting:** Subgroup analysis of female subjects with acne vulgaris receiving active treatment enrolled in two randomized, double-blind Phase 3 clinical trials. **Treatment:** Twice-daily applications of dapsone 5% gel over 12 weeks. **Participants:** Adolescent (12–17 years of age) and adult (≥18 years of age) females. **Measurements:** At baseline and at Weeks 2, 4, 6, 8, and 12, subjects were evaluated using the global acne assessment score and by counts of inflammatory, noninflammatory, and total acne vulgaris lesions. Adverse events were monitored. **Results:** A total of 347 adolescent and 434 adult women were included in the subgroup analysis. At Week 12, dapsone 5% gel significantly reduced mean global acne assessment score in both subgroups ($p<0.001$); however, the proportion of subjects with clinical success (no or minimal acne based on global acne assessment score) at Week 12 was greater in adult women (53.5%) versus adolescent females (45.3%, $p=0.022$). Significantly greater percentage reductions in both noninflammatory ($p<0.0001$) and total lesion counts ($p=0.0008$) were observed in the adult group as compared to the adolescent group. Percentage reductions from baseline in inflammatory lesions were similar in both groups. No major safety issues and no previously unrecognized safety signals were noted. **Conclusion:** This subgroup analysis of female patients indicates that dapsone 5% gel twice daily is effective in reducing inflammatory and noninflammatory acne vulgaris lesions in both adolescent and adult women, and is safe in these subgroups. Overall, these data suggest that efficacy of dapsone 5% gel twice daily for facial acne vulgaris may be greater in the adult female population. (*J Clin Aesthet Dermatol.* 2015;8(1):31–37.)

Acne vulgaris (AV) in adult women has been receiving increased attention both in the United States and globally, as the frequency of office visits for AV affecting post-adolescent women appears to be increasing.[1] A survey of 1,013 respondents in the United States showed that 51, 35, and 26 percent of women report having AV in their 20s, 30s, and 40s, respectively.[2] Additionally, AV is common in adult women of all ethnicities, skin types (oily, dry, combination, sensitive), and skin colors (Fitzpatrick skin type I–VI); both visibly noninflammatory lesions (i.e., comedones) and visibly inflammatory lesions (i.e., papules, pustules)

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are found in both adolescent females and adult women with AV; and the anatomic distribution of AV is similar overall in both subpopulations.[3–7] Available data and clinical observation have shown that the relative quantities of facial AV lesion types (i.e., comedones, papules) overlap among patients in both age-related subsets.[3–7] Although a U-shaped pattern of predominantly inflammatory papules involving the lower cheeks, jawline, and anterior and lateral neck has been noted in some adult women with AV, and it has been stated that AV in adult women presents predominantly as inflammatory lesions, it has been reported that approximately three-fourths of adult women with AV present with a mixed pattern of comedonal and inflammatory facial acne lesions that are often found more diffusely on the face and not just in the U-shaped region.[1,4–8]

It is important for the clinician to consider the possibility of underlying disorders that cause androgen excess in adult women presenting with AV; however, the majority exhibit normal values when laboratory testing is performed.[1,5,6,9,10] Most of the discussions about treatment of AV in adult women focus on the use of systemic therapies, such as oral contraceptives and spironolactone, with little emphasis on topical therapies.[5,6,9–11] Overall, controlled trials evaluating the efficacy and safety of topical agents specifically in adult women with AV are lacking, with subgroup analyses completed with only a few therapeutic agents and formulations.[6,8]

Dapsone is a sulfone derivative that has been reported to demonstrate a variety of anti-inflammatory properties.[12,13] When applied topically to the face twice daily, dapsone 5% gel was found in clinical studies to be effective for AV for at least 12 months.[14,15] In two large Phase 3, double-blind, randomized, vehicle-controlled, 12-week trials in subjects ≥12 years of age with facial AV, dapsone 5% gel applied twice daily proved to be superior to vehicle gel in reducing inflammatory, noninflammatory, and total lesions from baseline.[14] No differences in adverse events (AEs) were observed between the dapsone-treated and vehicle-treated study groups. The outcomes of these Phase 3 studies led to the approval of dapsone 5% gel twice daily for AV by the United States Food and Drug Administration (FDA) in 2005.

A subgroup analysis of outcomes in men compared with women from the two Phase 3 trials demonstrated that efficacy and tolerability were favorable in both sexes.[14] However, a subgroup analysis showed significantly greater reductions in inflammatory lesions ($p<0.0001$), noninflammatory lesions ($p<0.0001$), and total AV lesions ($p<0.0001$) in both the actively treated and vehicle-treated study arms in females (n=1520) compared with males (n=1378).[16] The percentage of subjects achieving endpoint success (clear or almost clear) based on global acne assessment score (GAAS) was statistically significantly superior in females compared with males in both the dapsone-treated study arm ($p=0.0003$) and the vehicle-treated study arm ($p=0.0013$).[16]

In this manuscript, the authors report the outcome of a subgroup analysis from the two Phase 3 pivotal trials in female subjects with facial AV treated with dapsone 5% gel or vehicle in two age-based subgroups, adolescent (12–17 years of age) and adult (post-adolescent; ≥18 years of age) females. The authors hypothesized before completion of this subgroup analysis that the response to dapsone 5% gel would be similar in efficacy and safety in both the adolescent and adult female populations for facial AV.

MATERIALS AND METHODS

Study design and participants. This subgroup analysis was based on data from two identically designed 12-week, multicenter, randomized, double-blind Phase 3 studies of dapsone 5% gel twice daily versus vehicle gel (n=3,010), as described previously.[14] Subjects (≥12 years of age) were randomly assigned to either treatment and instructed to apply the test material twice daily to the face after washing with a standardized soap-free cleanser. Subjects included in the trials had clinically diagnosed AV, with 20 to 50 inflammatory lesions and 20 to 100 noninflammatory lesions located on the face above the mandibular line at baseline. Subjects were excluded if severe cystic acne or conglobate acne was present or if any emerging nodular lesions above the mandible were noted. Subjects were also excluded if they used other treatments (i.e., topical, systemic, devices) that could affect AV, including the use within four weeks of baseline of any systemic or immunosuppressive agents or other therapies known to affect AV or inflammatory responses and/or the use of oral isotretinoin within three months of baseline. Women of childbearing potential could not be pregnant or nursing and had to be using an effective form of contraception as determined by the investigator. Women taking oral contraceptives were required to have been using them for at least three months prior to study entry. To be included in this subgroup analysis, female subjects treated with dapsone 5% gel twice daily and vehicle gel were stratified by age: ≥18 years (adult or post-adolescent) and 12 to 17 years (adolescent).

Study visits and assessments. Enrolled subjects were evaluated at baseline and at Weeks 2, 4, 6, 8, and 12. At each visit, all subjects underwent investigator global assessment using GAAS and counting of inflammatory and noninflammatory AV lesions, along with the total AV lesion count.[14] The GAAS was scored on a 5-point scale (0=none, 1=minimal, 2=mild, 3=moderate, and 4=severe).

Efficacy assessments. Efficacy at the 12-week time point (study endpoint) was assessed by comparing the mean GAAS score at baseline and at study endpoint as well as change from baseline. In addition, efficacy was evaluated based on the proportion of subjects achieving success on GAAS, defined as achieving a rating of none (0) or minimal.[1] Efficacy was also determined via acne lesion counts. Endpoint success for AV lesions was defined as a significantly greater mean percentage reduction from baseline in at least two of the three types of AV lesions (inflammatory, noninflammatory, total) at Week 12.

Tolerability and safety monitoring. AEs, including

signs and symptoms of application site reactions (local skin tolerability), were monitored and captured throughout the study at each study visit or if reported otherwise by the study subject.

STATISTICAL METHODS

Within-group change from baseline was analyzed and comparisons were performed using the Wilcoxon signed-rank test. Ranked analysis of covariance was used to analyze the percentage of reduction in acne lesion counts.

RESULTS

Subject disposition and characteristics. Among the 2,507 evaluable subjects who completed the two Phase 3 pivotal trials, 781 female subjects in the dapsone 5% gel group, (n=347, adolescent girls 12–17 years of age; n=434, adult women ≥18 years of age) were eligible for this analysis (Table 1). The mean age of the adolescent subgroup was 14 years and the mean age of the adult subgroup was 27 years. Most subjects were white, with race/ethnicity definitions and their dispositions outlined in Table 1. At baseline, no difference was noted between groups in GAAS scores. Mean numbers of AV lesions were higher at baseline in the adolescent subgroup by 1.5 inflammatory lesions, 7.8 noninflammatory lesions, and 9.2 total lesions; however, the standard deviation ranges indicate that there was considerable overlap in lesion types and quantities between both age-related female subgroups.

TABLE 1. Demographics and clinical characteristics at baseline

CHARACTERISTIC	ADOLESCENT FEMALE GROUP (12–17 YRS OF AGE) [n=347]	ADULT FEMALE GROUP (≥18 YRS OF AGE) [n=434]	*p* VALUE
Age, yrs, mean ± SD (range)	14.4 ± 1.6 (12–17)	27.4 ± 7.8 (18–63)	<0.001
Race/ethnicity, n (%)			
White[a]	266 (76.7)	267 (61.5)	0.0001
Black	50 (14.4)	106 (24.4)	
Hispanic	27 (7.8)	42 (9.7)	
Asian	1 (0.3)	13 (3.0)	
Multiracial[b]	1 (0.3)	3 (0.7)	
Other[c]	2 (0.6)	3 (0.7)	
GAAS*	2.5 ± 0.6	2.5 ± 0.6	0.2
Inflammatory lesions	29.0 ± 8.9	27.5 ± 8.1	0.0233
Noninflammatory lesions	50.1 ± 22.5	42.3 ± 23.4	<0.0001
Total lesions	79.0 ± 26.6	69.8 ± 25.9	<0.0001

Data are reported as mean ± SD unless otherwise indicated.
*GAAS=global acne assessment scale
[a]Arabic, Armenian, eastern European, Egyptian, Palestinian, South American, Turkish, white
[b]Biracial, black/white, and black/Hispanic
[c]Brazilian, Indian, Métis, Native American, Asian Indian, East Indian, and Mulatto

Efficacy. At Week 12, dapsone 5% gel improved AV in both the adolescent and adult female subgroups, as demonstrated by significantly reduced mean GAAS in both subsets ($p<0.001$) (Figure 1A). However, the proportion of subjects with clinical success (GAAS score 0 or 1) at Week 12 was greater in adult women (53.5%) versus adolescents (45.3%, $p=0.022$; Figure 1B). Dapsone 5% gel significantly reduced mean GAAS from baseline ($p<0.001$) in both groups, with no differences in mean change from baseline to Week 12 in GAAS between dapsone-treated adolescent girls and adult women (Figure 1C). Both groups showed significantly greater mean changes from baseline in GAAS than their vehicle-treated counterparts: for adolescents, dapsone 5%: –0.85; vehicle: –0.67 ($p=0.0187$); for adults, dapsone 5%: –0.94; vehicle: –0.80 ($p=0.0426$).

Treatment with dapsone 5% gel resulted in statistically significant reductions in inflammatory, non-inflammatory, and total lesion counts expressed as percentage change from baseline in both adolescent females and adult women (Table 2). The percentage changes from baseline in all lesion endpoints were numerically greater for each type of lesion in adult women compared with adolescent females. In the dapsone 5% gel study arm, statistically significant lesion reductions were observed in the adult-group compared with the adolescent-group for both noninflammatory ($p<0.0001$) and total lesion counts ($p=0.0008$).

Tolerability and safety. Facial application of dapsone 5% gel for 12 weeks reduced (improved) the percentage of subjects reporting erythema, dryness, oiliness, and peeling compared with baseline in both adolescent and adult females (Figure 2). These results did not reveal any differences from findings observed in the full population of subjects in the two pivotal Phase 3 trials.[14] This current analysis of AE data from both female subgroups showed no major safety issues, and no previously unrecognized safety signals were observed.

DISCUSSION

Dapsone 5% gel applied twice daily for facial AV has demonstrated efficacy and safety in both male and female subjects based on outcomes reported from two double-blind, randomized, vehicle-controlled, 12-week trials and has also been shown to exhibit a greater clinical success rate in females compared with males.[14,16] The subgroup analysis reported here was designed to compare the efficacy of dapsone 5% gel applied twice daily in two subgroups of

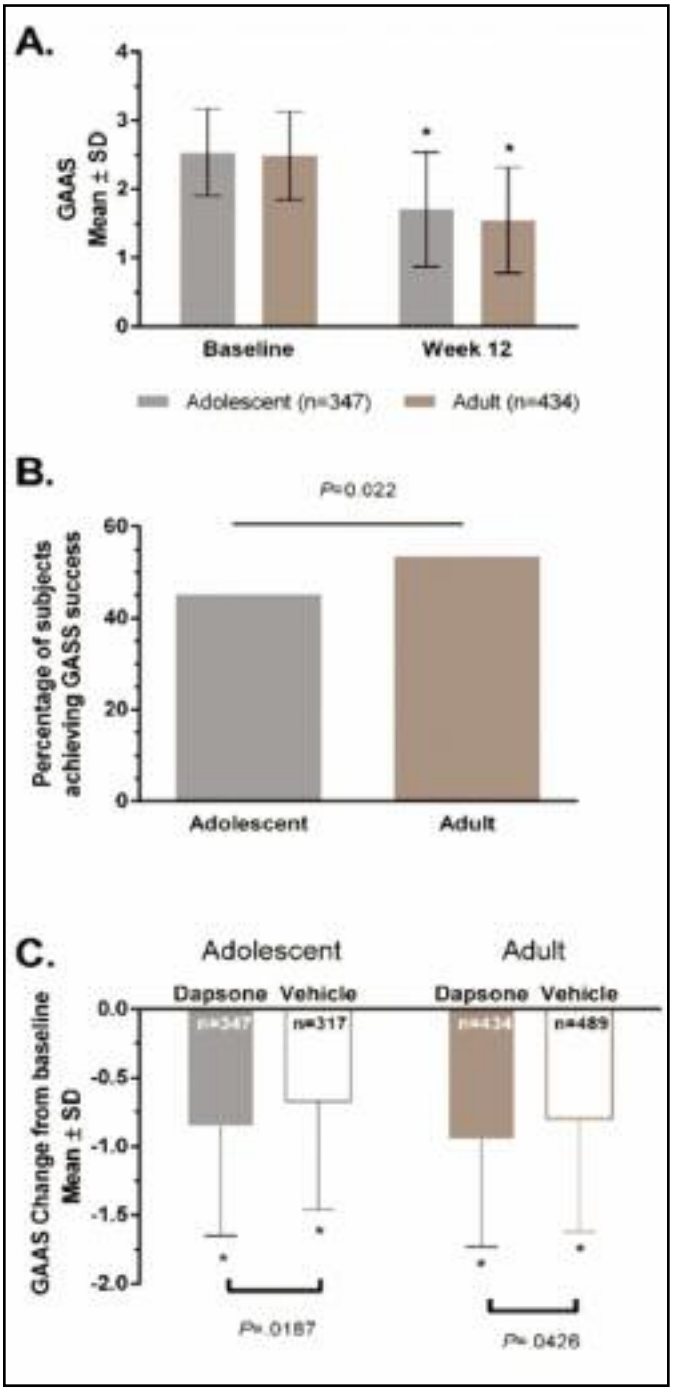

Figure 1. Efficacy of dapsone 5% gel in adolescent and adult females with acne vulgaris. (A) GAAS rating at baseline and Week 12. (B) Percentage of dapsone 5% gel-treated subjects achieving GASS success (score 0 or 1) at Week 12. (C) Mean change from baseline in GAAS in dapsone 5% gel and vehicle gel-treated subjects
GAAS=global acne assessment scale. *p<0.001 vs. baseline

female patients based on age: adolescents (12–17 years of age) and adults (≥18 years of age). The results of this subanalysis demonstrated that dapsone 5% gel was effective in both adolescent and adult females in reducing facial AV. A comparable reduction was observed in inflammatory AV lesions in both adult and adolescent females, whereas reductions in noninflammatory and total AV lesions were greater in adult women compared with adolescents. These data suggest that the efficacy of dapsone 5% gel applied twice daily for facial AV, although shown to be effective in females aged ≥12 years, may exhibit greater efficacy overall in adult women (≥18 years of age) compared with adolescent females (12–17 years of age). Tolerability and safety were highly favorable in both subgroups.

GAAS responder rates in both adolescent (45.3%) and adult females (53.5%) were greater than the overall responder rate (40.5%) reported from the combined male and female population in the pivotal Phase 3 studies, further supporting that dapsone 5% gel was more effective in females overall.[14,16] Dapsone 5% gel was equally effective in both age groups in reducing the percentage change from baseline in inflammatory lesions. Interestingly, although adolescent females had significantly greater numbers of both inflammatory and noninflammatory AV lesions at baseline than did adult women enrolled in the study, dapsone 5% gel was more effective in reducing noninflammatory lesions in adult women compared with reductions noted in the adolescent female group.

One limitation of this analysis is similar to limitations of other age-based subgroup analyses completed with topical agents used to treat AV.[6–8] The age ranges that define the dividing line to separate the AV subgroups in females have been arbitrarily selected in both previous literature and in subgroup analyses of data from pivotal studies. They have not been derived from any established scientific basis to differentiate age-based subgroups. Nevertheless, a dividing line needs to be selected to create a reasonable frame of reference for analysis and discussion. In this subanalysis, the age of 18 years was used as the line dividing adolescent and adult females into two subgroups, with the recognition that this parameter has been used previously to divide these same subgroups.[7]

A second limitation of this subgroup analysis is that the comparison of efficacy outcomes between the age-based subgroups was focused on data obtained only from females actively treated with dapsone 5% gel. The primary design of the subgroup analysis was not focused on outcomes in adolescent and adult females treated with vehicle gel; however, results observed in vehicle-treated adult women and adolescents were also documented and reported. Dapsone 5% gel has been demonstrated to be more effective than vehicle gel in improving AV in the overall population of enrolled subjects, which included females and males ≥12 years of age.[14] Outcomes noted in the vehicle-treated female subjects for both age-based subgroups (adolescents and adults) are depicted in Figure 1C and Table 2.

Across all ethnic groups, AV is the most common diagnosis seen in dermatology ambulatory practice in the United States, with approximately two-thirds of visits for AV made by females and one-third of visits for AV made by women >25 years of age.[17,18] Although teenagers are the most common group affected overall, more than 50 percent of females with AV are over the age of 20 years.[2,4,19]

Approximately three-fourths of adult women with AV have had the disorder as an adolescent, although the severity as an adult may be more severe, the same, or less severe than in the past.[1,4–6] The remaining one-fourth of adult women with AV experienced onset of the disorder after adolescence. If an underlying cause of androgen excess is identified, therapy needs to be directed at treating that disorder. However, most adult women with AV do not have an identifiable underlying disorder and are treated with a variety of conventional therapies for AV, often with oral contraceptives and/or oral spironolactone.[1,5,6,9–11,20] Unfortunately, topical therapy in adult women with AV has not received much direct research to determine whether specific agents and/or vehicle formulations are generally preferred due to more favorable efficacy and/or tolerability.

With regard to topical therapy, skin color, often reported as the Fitzpatrick skin phototype, is frequently addressed as an important clinical consideration because of concern regarding persistent residual hyperpigmentation that may be caused by resolved inflammatory AV lesions and/or skin irritation from topically used products.[21,22] In addition, some adult women with AV present with inflammatory AV lesions located below the jawline, involving the submandibular and lateral neck regions, which are sites more prone to irritation from topical medications used to treat AV.[1,5,6,9,10] Certain active ingredients used in topical acne medications (i.e,. benzoyl peroxide, retinoids, salicylic acid) or vehicles that have a propensity to induce cutaneous irritation require more cautious use when applied on the neck and/or to the lower face, especially the perioral region.[11]

TABLE 2. Percentage (%) change from baseline in acne lesion counts (Week 12)

LESION TYPE (MEAN % ± SD)	TREATMENT ARM	% CHANGE ADOLESCENT FEMALE GROUP (12–17 YRS OF AGE)	% CHANGE ADULT FEMALE GROUP (≥18 YRS OF AGE)	*p* VALUE[a]
Inflammatory lesions	Dapsone Vehicle	–56.2 ± 33.3 –48.0 ± 40.6	–60.0 ± 33.3 –56.8 ± 34.7	0.3
Noninflammatory lesions	Dapsone Vehicle	–35.5 ± 41.8 –23.5 ± 48.8	–47.4 ± 38.6 –42.3 ± 35.6	<0.0001
Total lesions	Dapsone Vehicle	–44.0 ± 32.7 –33.7 ± 35.8	–52.8 ± 29.7 –48.3 ± 30.3	0.0008

[a]Comparison between age groups
Adolescent females: dapsone treated, n=347; vehicle treated, n=317
Adult women: dapsone treated, n=434; vehicle treated, n=489

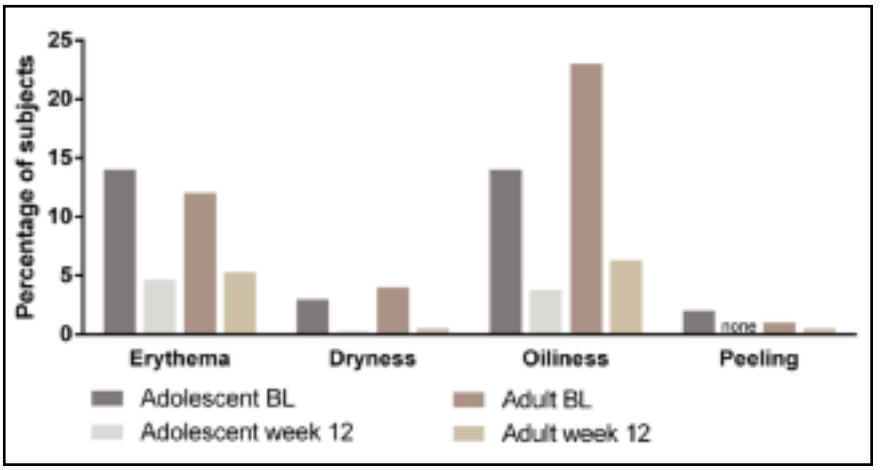

Figure 2. Dapsone 5% gel effect on tolerability in adolescent and adult females with acne vulgaris; BL=baseline

Although AV in adult women may be responsive overall to many of the conventional therapies used to treat patients of either gender, some differentiating considerations need to be taken into account when treating adult women with AV, which are important to address in how they may or may not apply to each affected woman.[1,3–5,10,23] Some of the major factors that are important to consider and attempt to differentiate when managing AV in adult women are outlined in Table 3.

It is important to take into account with each patient her age and phase in life. Women who are in their 20s, 30s, and beyond are often frustrated and embarrassed by having AV, a facial skin condition that they thought would never persist after the teenage years or even begin later in life.[23] Many have the stress of balancing time-consuming responsibilities, such as family, children, and/or full-time employment. As AV most often involves the face, it is not uncommon for adult women with AV to feel self-conscious, less attractive, and less willing to interact socially or professionally, as the presence of AV lesions adversely affects their self-image and self-esteem.[5,23]

A survey of adult women with AV (N=409) indicated 54 percent used ≥3 treatments for AV over the past year, with 74 percent indicating that they want treatment for their AV that has been shown to be effective for adult females; many also report that it is important for the clinician to explain their options for treatment and involve them in the decision.[6,23] Dedicating time to obtain a detailed history and to carefully evaluate the skin of the patient is important to adult women who are seeking treatment for AV. From a clinical perspective, a practical "checklist" of important characteristics that may be helpful during evaluation of each adult woman who presents with AV includes psychosocial

TABLE 3. Acne vulgaris (AV) in adult women: Differentiating factors that can impact management of individual cases[a]

FACTOR	CLINICAL IMPLICATIONS IN ADULT WOMEN WITH ACNE VULGARIS (AV)
Prior experience with AV	• 3/4 have experienced AV as a teenager • 3/10 stated their AV is worse as an adult • 5/10 have used >3 products for AV within the past 12 months • 5/10 have not seen a dermatologist within the past 3 years
Psychosocial issues	• 3/4 frustrated with thinking about or seeing their AV • 3/4 feel they will never understand why they have AV as an adult • 6/10 feel others do not understand how it feels to have AV as an adult • 1/3 embarrassed to discuss their AV with a dermatologist as it is a teen issue • Many use makeup to cover up or divert attention from AV lesions
Attitudes and expectations as an adult woman with AV	• 6/10 would "understand that AV will not clear up overnight" • 3/4 stated they could tell if a prescription medication is working in ≤2 weeks; 4/10 stated they could tell within 1 week • More than 8/10 stated they would like dermatologist to recommend prescription therapy for AV when at an office visit unrelated to AV • 1/3 want a discussion of treatment options by the dermatologist • 3/4 indicated they want treatment proven to work for AV in adult women

[a]Sources from European and US publications; surveys completed by women with AV aged >25 years of diverse ethnicities and skin color with >25 "facial pimples" (N=617)
References 1,6,23

factors; first age of onset of AV (including any history of adolescent AV); attitudes and expectations about having AV later in life; attitudes and expectations about treatment of AV later in life; current AV lesion types; anatomic distribution (i.e., face, neck, trunk); overall time course of AV (any flare patterns); presence of acne scarring; presence of dyschromia (persistent inflammatory erythema or hyperpigmentation); previous and current prescription and/or over-the-counter (OTC) therapies used for AV; use of physical modalities and/or device therapies (i.e., facials, peels, microdermabrasion, light therapies, home use devices); current or previous use of hormonal agent(s) (oral contraceptives, spironolactone, intrauterine or implanted devices, injectable agents); signs and/or symptoms of androgen excess (i.e., hirsutism, alopecia, irregular menses, missed menses, inability to conceive a child); medical history; current medications and any OTC supplements; diet; and pregnancy considerations.

CONCLUSION

The topical treatment of AV in adult women has received little attention until recently. Importantly, this patient population is characterized by specific challenges, many caused by the presence of AV at a later stage in life, which most women do not expect to occur. Feelings of frustration and embarrassment are common, and the desire for therapies that are effective and well-tolerated specifically in this population is commonly expressed.

Dapsone 5% gel applied twice daily for facial AV has been shown to be effective and safe in male and female subjects ≥12 years of age in pivotal Phase 3 trials and in a 12-month study in which ~80 percent of subjects used dapsone 5% gel twice daily as monotherapy over the duration of the study.[14,15] More recently, data analysis from the Phase 3 pivotal trials has shown greater efficacy in female than in male subjects.[16] The subgroup analysis data reported here, based on female patients actively treated with dapsone 5% gel twice daily, support that this agent is effective, well-tolerated, and safe in both adolescent and adult females, and further suggests that efficacy may be greater in the latter subgroup.

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