AZELAIC ACID 15% GEL ONCE DAILY VERSUS TWICE DAILY IN PAPULOPUSTULAR ROSACEA

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Abstract

Background: Twice-daily azelaic acid (AzA) is the conventional regimen for papulopustular rosacea, but once-daily AzA may be equally effective, with greater convenience and dosing flexibility. In order to test this hypothesis, an exploratory study was conducted.

Methods: The evaluable efficacy population of this 12-week double-blind, parallel-group study included 72 patients and the population that was used to report safety results included 92 patients. Baseline characteristics were comparable between the once-daily and twice-daily study groups. Evaluations were performed at baseline and at weeks 4, 8, and 12.

Results: No significant difference was found between the once-daily and twice-daily groups at the end of study therapy in mean investigator global assessment (IGA) scores, treatment success, or treatment response. The mean number of inflammatory lesions, the intensity of erythema intensity, and the intensity of telangiectasia at treatment end were likewise not significantly different ($P>.205$ for all). More than 90% of subjects in each group rated cosmetic acceptability of this AzA gel as satisfactory or better.

Conclusion: Based on these findings and those of prior studies, once-daily AzA 15% gel can therefore be utilized as a safe, effective, and economical dosing option for the treatment of mild-to-moderate papulopustular rosacea. Once-daily dosing of AzA 15% gel was well accepted by patients and can offer considerable dosing flexibility and convenience for the patient as well as for the dermatologist.

Introduction

Rosacea is a common, chronic, relapsing cutaneous disorder that is reported to affect more than 1 in 20 individuals in the US.[1] It is characterized by a variety of central facial signs and symptoms and can be classified into 4 main subtypes: erythematotelangiectatic, papulopustular, phymatous, and ocular.[2] In most patients, combinations of signs and symptoms from 1 or more subtypes appear in a pattern of exacerbation and remission.[2] Recently, it has been suggested that the inflammatory changes in rosacea may be due to an increased activity of antimicrobial peptides in facial skin.[3]

Current treatment is directed at reduction of symptoms and includes topical agents and systemic antibiotics.[4] One of the most effective topical treatments for mild to moderate papulopustular rosacea is azelaic acid (AzA), a naturally occurring dicarboxylic acid that has proven anti-inflammatory effects, as well as antikeratinizing and antimicrobial action, although its mechanism of action in rosacea is not well understood.[5-8] Azelaic acid 15% aqueous gel was approved for mild to moderate papulopustular rosacea in the US in 2002 and in the European Union in 2003—the first new drug class to be approved for rosacea in more than a decade.[6] Among the advantages offered by the micronized solubilized 15% gel formula over the previously used 20% cream formulation (indicated for the treatment of mild to moderate acne vulgaris) are improved drug release and better absorption.[6]

Although the labeled dosage of AzA 15% gel is twice daily in the US,[5] a once-daily regimen is sometimes used in clinical practice.[9] A single daily dose appears desirable by offering additional dosing convenience without loss of efficacy. Therapeutic failure may reflect problems with adherence to a prescribed therapy regimen and is not necessarily overcome by increasing the number of daily doses. A number of studies involving different medication classes have indicated that patient compliance was apparently inversely related to the frequency of dosing.[10-14] Conversely, however, it must also be taken into account that reducing the frequency of medication may yield poor therapeutic results if drug concentrations fall below the therapeutic threshold.

Azelaic acid 15% gel has consistently been proven safe and effective in patients with papulopustular rosacea,[15,16] but a once-daily AzA gel regimen, a clearly useful alternative, has not been carefully studied to date under controlled conditions. To address this issue, an exploratory multicenter, double-blind, parallel-group study of AzA 15% gel was conducted in patients with papulopustular rosacea to compare the safety and efficacy of a once-daily regimen with that of the conventional twice-daily treatment.

Materials and Methods

Patient Population

Patients for this multicenter study were drawn from 7 centers throughout the US. Eligibility requirements included subjects ages 18 years or older, clinically documented papulopustular facial rosacea (subtype 2 rosacea) with at least 10 and no more than 50 inflamed papules and/or pustules, persistent erythema, and telangiectasia. Subjects had to be willing and able to meet the study requirements of administering the drug over a 12-week period, comply with medical examinations, and maintain a drug diary to help assess treatment compliance. Persons included in the study were required to sign an institutional review board-approved informed consent document.

Treatment Regimen

Patients were randomized to receive either AzA 15% gel once daily (QD group) or AzA 15% gel twice daily (BID group) for a maximum of 12 weeks. To achieve double blinding, both groups received an morning and evening tube for each study day. The subjects in the QD group received 1 application of a gel vehicle each day in addition to 1 application of the study drug. Preceding and concomitant treatments were controlled by a washout period and exclusion criteria. Following the baseline clinical evaluation, outcomes were monitored through follow-up evaluations at weeks 4, 8, and 12.

Compliance

Proper compliance with the treatment regimen was assessed by weighing all unused, partly used, and empty containers at the end of treatment. Additionally, adherence was measured by asking the patient to report missed doses of treatment and to maintain a usage diary in which they recorded dates and times of medication application.

Outcome Measures

Efficacy evaluations were primarily based on the Investigators' Global Assessment (IGA), which was scored on a 7-point static scale (0=clear, 1=minimal, 2=mild, 3=mild to moderate, 4=moderate, 5=moderate to severe, 6=severe).[15] The IGA was analyzed in terms of treatment success, with success defined as the sum of clear and minimal IGA scores and treatment response, with response defined as the sum of clear, minimal, and mild IGA scores. Further efficacy variables were the change compared to baseline in inflammatory lesion count, erythema intensity, and telangiectasis intensity. Erythema intensity and telangiectasis intensity were measured on a 4-point scale (1=none, 2=mild, 3=moderate, 4=severe). Other endpoints were investigators' and patients' assessments of overall improvement measured on 5-point scales (ranging from 1=excellent improvement to 5=deterioration or worse), patients' opinions about cosmetic acceptability expressed by 5 categories ("very good", "good", "satisfactory", "poor", "no opinion"), and patients' opinions about local tolerability expressed by 6 categories ("excellent", "good", "acceptable despite minor irritation", "less acceptable due to continuous irritation", "nonacceptable", and "no opinion"). The scoring of cosmetic acceptability and local tolerability were only indicated by categories; no numeric values were attached to those ratings.

Statistical Methods

The statistical analyses of scores and outcomes were mainly based on posttreatment data. For patients who dropped out before the end of the full 12-week treatment period, the last observations were carried forward (LOCF). Differences between treatments in success and response rates were compared by center-adjusted Cochran-Mantel-Haenszel (CMH) tests with modified ridit scores. Changes in inflammatory lesion count versus baseline were analyzed using a covariance model (ANCOVA) that contained fixed-effect terms for the treatment group, study center, and baseline lesion count as covariates. Study centers that randomized fewer than 10 patients were pooled for analysis. All other efficacy parameters were compared for treatment differences using Mantel-Haenszel type tests or Pearson χ^2 test as appropriate. For all statistical tests, a 2-sided 5% significance level was applied.

Results

Patients

Of 101 patients with mild-to-moderate papulopustular rosacea screened at 7 centers, 92 patients fulfilled eligibility requirements and were randomized, with 45 patients assigned to once-daily treatment and 47 to twice-daily treatment with AzA 15% gel. Efficacy results from 1 study center (20 patients) were considered nonevaluable because calculations of IGA assessments from that center inadvertently included data that were not in conformity with the study protocol. The evaluable efficacy population (EEP) therefore comprised 72 patients, including 35 assigned to the QD group and 37 to the BID group. Therapy was discontinued before study week 12 for 4 (2 from each study group) of the randomized EEP patients (5.6%): 1 patient never received the study medication; 1 patient withdrew consent; 1 was lost to follow-up; and another discontinued treatment for another, unspecified reason. All 92 randomized patients were included in the analyses of baseline characteristics and safety. Baseline characteristics of the subjects (Table 1) were similar across the 2 treatment groups ($P>.2$ for age, gender, and ethnic group).

Compliance was similar in the 2 treatment groups. At least 90% compliance was achieved as assessed by patient diaries of 41 patients (91.1%) in the QD group and by 44 patients (93.6%) in the BID group.

Efficacy

No significant difference was found in any efficacy endpoint in the comparison of patients receiving once-daily AzA 15% gel with those receiving twice-daily treatment ($P>.05$ for all comparisons). The IGA scores at the end of treatment were statistically similar in the QD and BID groups (center-adjusted CMH analysis of variance [ANOVA], $P=.8402$) (Table 2). Correspondingly, IGA-based response rates did not differ significantly between the study groups. At week 12, response to treatment was achieved in 64.5% of the QD group and 68.8% of the BID group (Pearson χ^2 test; $P=.7215$), whereas

the posttreatment response rates (LOCF) were 57.1% in the QD group and 59.5% in the BID group (center-adjusted CMH test; *P*=.8190) (Figure 1). Equivalent treatment success was observed in 37.5% of the QD group versus 40.5% of the BID group at the end of treatment (center-adjusted CMH test; *P*=.7887).

Both the once-daily and twice-daily treatment regimens led to a similar substantial decrease in the number of inflammatory lesions over the study period (Figure 2), with no efficacy plateau at the end of the study period. In the QD group, the mean number of inflammatory lesions decreased from 18.2 (±8.3) to 6.6 (±6.5) by the end of treatment. A similar reduction, from 19.8 (±7.6) to 6.0 (±7.0), was reported in the BID group. The corresponding mean reduction in inflammatory lesions was 63.3% in the QD group versus 71.1% in the BID group, with no significant difference between the groups in either nominal lesion count reduction (ANCOVA, *P*=.3028) or percent reduction (ANCOVA, *P*=.2299).

Treatment with AzA 15% gel led to a decrease in the intensity of erythema over the course of the study with no statistically significant differences between the QD group and BID group (center-adjusted CMH ANOVA, *P*=.9666).

The severity of telangiectasia scores remained largely unaltered in most patients over the study period, and a change towards improvement was seen in no more than 14.3% of the QD patients and 13.5% of the BID patients. The changes from baseline were not significantly different in the 2 groups (center-adjusted CMH ANOVA, *P*=.3459).

Cosmetic acceptability of the AzA 15% gel was high. Acceptability of the gel was rated very good or good (the 2 highest ratings) by 87.9% of the QD group and by 86.2% of the BID group. Overall, more than 90% of patients in each group rated the cosmetic acceptability as satisfactory or better. No statistically significant difference was found between the treatment groups (Pearson χ^2 test; *P*=.9572).

Investigators gave the QD and the BID groups equivalent ratings in overall improvement at the end of study. Overall improvement was rated as excellent or marked in 64.7% of patients receiving AzA gel once daily, compared with 57.1% of those receiving AzA gel twice daily (Figure 3). Again, although surprisingly more QD than BID patients received ratings of excellent or marked improvement, the end-of-treatment difference between groups was not significant (Wilcoxon rank-sum test; *P*=.3574).

Table 1. Demographic characteristics of population at baseline randomized to Azelaic acid (AzA) 15% gel once daily (QD) or twice daily (BID).

Characteristic	QD Group	BID Group	*P* value
Randomized (n)	45	47	
Evaluable efficacy population* (n)	35	37	
Mean age, years (±SD)	48.5±13.2	49.6±12.0	0.6935†
Gender	n (%)	n (%)	0.2218§
Female	34 (75.6)	30 (63.8)	
Male	11 (24.4)	17 (36.2)	
Race			0.3874§
Caucasian	42 (93.3)	46 (97.9)	
African American	1 (2.2)	0 (0)	
Hispanic	0 (0)	1 (2.1)	
Asian	1 (2.2)	0 (0)	
Other	1 (2.2)	0 (0)	

*One study center was not evaluable in regard to efficacy (assessments not in conformity with protocol); all patients were considered in the safety population; †Two-sided t test; §Pooled-center Pearson's χ^2 test.

Safety

Comparable rates of treatment-related cutaneous adverse events (AEs) were observed in both treatment groups. Thus, 18 of 45 (40%) patients of the QD group and 17 of 47 (36.2%) patients of the BID group reported at least 1 cutaneous

Table 2. Investigator's Global Assessment scores at end of treatment (Azelaic acid 15% gel).

Rating	QD Group (n=35): n (%)*	BID Group (n=37): n (%)*
0: clear	2 (5.7)	4 (10.8)
1: minimal	11 (31.4)	11 (29.7)
2: mild	7 (20.0)	7 (18.9)
3: mild to moderate	9 (25.7)	9 (24.3)
4: moderate	5 (14.3)	6 (16.2)
5: moderate to severe	1 (2.9)	0 (0.0)
6: severe	0 (0.0)	0 (0.0)
Center-adjusted CMH ANOVA *P* value	.8402	

*Findings from study dropouts were included as last observation carried forward.

Figure 1. Percentage of treatment response in once-daily and twice-daily azelaic acid (AzA) 15% gel recipients (*P*=.8190).

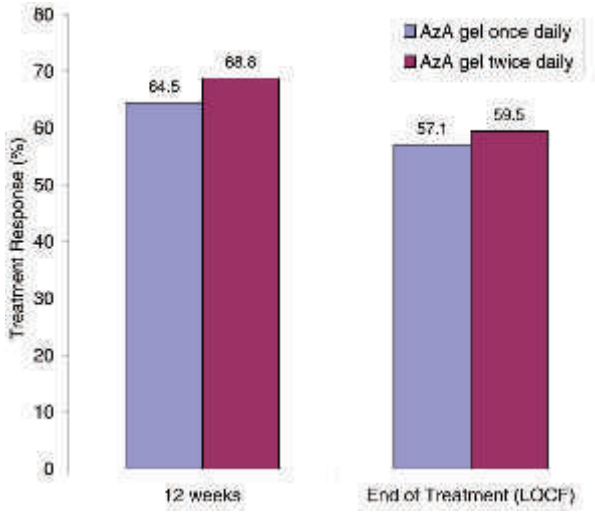
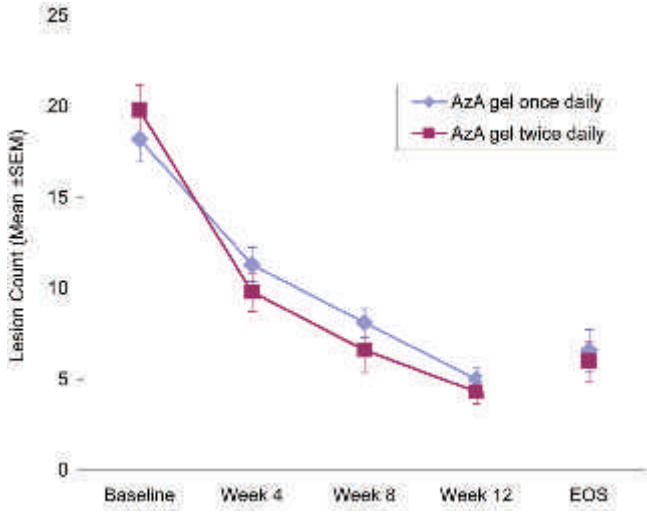


Figure 2. Mean facial inflammatory lesion count by week in once-daily and twice-daily azelaic acid (AzA) 15% gel recipients.



AE. The most common adverse skin symptoms were skin pain, pruritus, and sensation of burning (QD group=70.9%, BID group=89.2%). Other treatment-related cutaneous AEs, reported in no more than 2 patients in each group, included pustular acne, dry skin, erythema, rash, exfoliation, skin irritation, skin tightness, and urticaria. The majority of treatment-related cutaneous AEs were mild (QD group=72.2%, BID group=76.4%).

Most treatment-related AEs were transient rather than persistent in nature (QD group=83.8%, BID group=70.5%). Severe treatment-related AEs were reported in 2 subjects in the QD group (4.4%) with none reported in the BID group. No phototoxic or photoallergic reactions were reported during the study. There were no serious causally-related AEs from the study medication. No patient was hospitalized because of an adverse event, and no patient discontinued the study medication because of an adverse event.

In the 2 groups, total tolerability ratings were not significantly different (Pearson's χ^2 test; *P*=.2995). At the end of treatment, a majority of the patients rated local tolerability of AzA gel as good or excellent (QD group=67.5%, BID group=77.8%). Four (9.3%) QD patients and 1 (2.2%) BID patient rated AzA therapy as "less acceptable due to continuous irritation." Two patients in the BID group rated tolerability as nonacceptable (4.4%).

Discussion

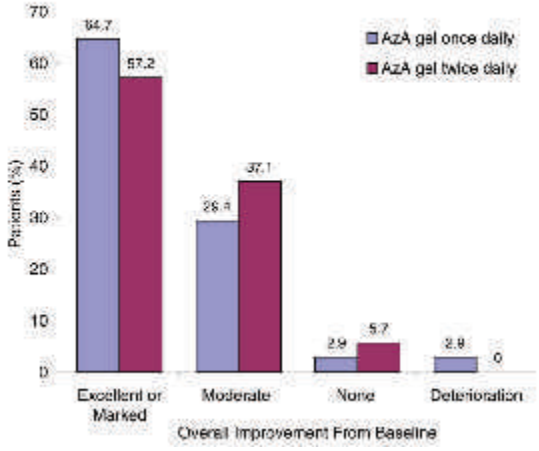
The aim of this study was to establish the clinical benefit of a once-a-day treatment regimen with AzA 15% gel in papulopustular rosacea. AzA 15% gel is a well-recognized medication for rosacea that has been approved in the US and major European countries for this indication. Its current approved usage, twice daily, is a standard regimen for many topical agents. However, because rosacea is a chronic condition that requires long-term use of treatment, patients over time may become progressively noncompliant with treatment. That may lead to poor therapeutic responses and ultimately increase the cost of care. Therefore, simplifying the treatment regimen by reducing dosing frequency without loss of therapeutic efficacy is a highly desirable therapeutic option that may considerably increase dosing flexibility and convenience.

It is generally anticipated that clinical efficacy will be paralleled by the frequency of dosing—that is, drugs will work poorly in patients who use less drug than prescribed and not at all in patients who take no drug, and, conversely, that better efficacy might be achieved by simply increasing the dosing frequency. That assumption holds true if the prescribed drug regimen is close to optimal and poor adherence to therapy plays no major role. However, studies of various diseases and treatment modalities have shown that the effectiveness of complex treatment regimens, including the frequently used twice-daily (morning/evening) dosing schedule, may be compromised by poor adherence.[11-14] Studies of psoriasis therapy including both topical and oral therapies have found adherence to be 70% to 82% with a once-daily regimen versus 17% to 44% with a twice-daily regimen.[17,18] Topical therapy is by nature particularly prone to nonadherence because of the possibility of improper application and underdosage or overdosage.[19,20]

The results of the current exploratory study support the previously proven benefit of AzA 15% gel twice daily and demonstrate an equivalent efficacy and safety of the novel once-daily treatment regimen.

In terms of efficacy, both once-daily and twice-daily regimens were associated with continued improvement in IGA scores and mean inflammatory lesion counts throughout the study period with no plateau over time. Moderate, marked, or excellent overall improvement was observed in >90% of patients in both groups at the end of treatment. No significant treatment differences were found in IGA scores or in IGA-derived treatment response (combining IGA scores of clear, minimal, and mild); response was 57.1% for QD and 59.5% for BID treatment.

Figure 3. Investigator rating of overall improvement from baseline to end of study in once-daily and twice-daily azelaic acid (AzA) 15% gel recipients (*P*=.3574).



The efficacy results for the BID group in the present study closely correspond with those observed in previous controlled rosacea trials of twice-daily AzA 15% gel versus vehicle and metronidazole.[15,16] The design and endpoints of those multicenter, double-blind, randomized, parallel-group studies were similar to those of the current study, allowing comparisons. For example, the 59.5% frequency of IGA-based treatment response in the present BID group did not differ substantially from those in the 2 vehicle-controlled studies (61% and 62%, respectively) and was slightly lower than in the comparison with metronidazole (69%). The duration of treatment in that study was 15 weeks compared to 12 weeks in this study.[15,16] Reductions in lesion count and baseline erythema in this trial were comparable to those in the phase 3 pivotal vehicle-controlled studies.[15,16]

The consistency of results for the BID treatment groups across the controlled studies reinforces the reproducibility of the efficacy of AzA 15% gel in papulopustular rosacea and thus strengthens the reliability of the efficacy findings for the once-daily treatment regimen.

Compliance with both regimens was high; a potentially lower compliance with the BID regimen could not be verified in this study. More than a 90% compliance was claimed by 91.1% of patients in the AzA once-daily group and by 93.6% in the AzA 15% gel twice-daily group. It must be emphasized that assessment of compliance by such means as diaries, medication tube weights, and elicited reports of missed doses tends to overestimate adherence, because patients whose compliance is being monitored are more likely to follow the dosing schedule than patients whose compliance is not being monitored. Nonetheless, the above results demonstrate that with good compliance, once-daily treatment with AzA 15% gel is a highly effective treatment alternative regimen in rosacea.

Occurrence of adverse effects is clearly one cause for nonadherence to medication and, subsequently, an increased risk of suboptimal treatment outcomes. The results of safety analysis showed that AzA is generally safe and well tolerated and did not indicate a negative effect of AEs on compliance. Thus, only a minority of patients (QD group: 31.4%, BID group: 29.7%) experienced cutaneous adverse events considered to be related to study treatment. No phototoxic or photoallergic reactions were reported. The most common cutaneous AEs were untoward sensory symptoms, such as skin pain, pruritus, and burning sensations, which may be related to the acidic properties of AzA. It is important to note that AEs were mild and transient in >70% of the total population. These AEs did not appear to be of major clinical concern to the patients, as no patient was hospitalized or discontinued the study medication because of an adverse event. By subjective overall assessment, only 5 patients (9.6% of the total), including 4 from the once-daily group, considered the local tolerability to be nonacceptable.

Cosmetic acceptability of the AzA 15% gel was similarly excellent in both groups, with >85% of patients giving the drug a good or very good rating (the 2 highest scores) and no patient designating cosmetic acceptability as poor.

In conclusion, this randomized, controlled trial demonstrated that a once-daily regimen of AzA 15% gel can parallel the effectiveness of a conventional twice-daily regimen in reducing IGA scores and lesion counts and producing continuing overall improvement in rosacea patients. An advantage of the proven efficacy of the once-daily regimen is that clinical benefit persists even in the event that patients are not fully adherent to a prescribed twice-daily regimen. The study also demonstrated a high degree of adherence with the once-daily regimen that was not impaired by any safety problems. Rather, both once-daily and twice-daily regimens had comparable and excellent safety and local tolerability, as well as excellent cosmetic acceptability. The once-daily AzA 15% gel regimen can therefore be considered as a safe, effective, economical, and well-accepted dosing option for the treatment papulopustular rosacea that considerably increases dosing flexibility and convenience for a wide range of rosacea patients who either do not require a twice-daily treatment regimen or who have trouble complying with multiple-dose regimens.

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Dr. Thiboutot has participated in clinical trials and has been a consultant/advisor for Intendis Inc, Galderma Laboratories LP, CollaGenex Pharmaceuticals Inc, Allergan Inc, Stiefel Laboratories Inc, and QLT Inc. Dr. Fleischer has participated in clinical trials and has been a consultant/adviser for Intendis Inc. Dr. Del Rosso has received grant/research support/honoraria from and has been a consultant/advisor and speaker for CollaGenex Pharmaceuticals Inc, Galderma Lab-

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References

1. National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). National Institutes of Health. US Department of Health and Human Services. What is Rosacea? Fast Facts: An Easy-to-Read Series of Publications for the Public. March 2005. Available at: http://www.niams.nih.gov/hi/topics/rosacea/FF_Rosacea.pdf. Accessed August 13, 2007.
2. Wilkin J, Dahl M, Detmar M, et al. Standard grading system for rosacea: report of the National Rosacea Society Expert Committee on the classification and staging of rosacea. *J Am Acad Dermatol.* 2004;50:907-912.
3. Yamasaki K, Di Nardo A, Bardan A, et al. Increased serine protease activity and cathelicidin promotes skin inflammation in rosacea. *Nat Med.* 2007;13:975-980.
4. Elewski BE, Fleischer AB Jr, Pariser DM. A comparison of 15% azelaic acid gel and 0.75% metronidazole gel in the topical treatment of papulopustular rosacea: results of a randomized trial. *Arch Dermatol.* 2003;139:1444-1450.
5. Finacea [package insert]. Pinebrook, NJ: Intendis Inc; 2005.
6. Bikowski JB, Goldman MP. Rosacea: where are we now? *J Drugs Dermatol.* 2004;3:251-261.
7. Akamatsu H, Komura J, Asada Y, et al. Inhibitory effect of azelaic acid on neutrophil functions: a possible cause for its efficacy in treating pathogenetically unrelated diseases. *Arch Dermatol Res.* 1991;283:162-166.
8. Elewski BE. Azelaic acid 15% gel for treatment of rosacea. *Expert Rev Dermatol.* 2006;1:535-545.
9. IMS National Disease and Therapeutic Index™. MAT 7/2006–6/2007 data: Finacea® applications.
10. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther.* 2001;23:1296-1310.
11. Guest JF, Davie AM, Ruiz FJ, Greener MJ. Switching asthma patients to a once-daily inhaled steroid improves compliance and reduces healthcare costs. *Prim Care Respir J.* 2005;14:88-98.
12. Stang P, Young S, Hogue S. Better patient persistence with once-daily bupropion compared with twice-daily bupropion. *Am J Ther.* 2007;14:20-24.
13. Kardas P. Comparison of patient compliance with once-daily and twice-daily antibiotic regimens in respiratory tract infections: results of a randomized trial. *J Antimicrob Chemother.* 2007;59:531-536.
14. Portsmouth SD, Osorio J, McCormick K, Gazzard BG, Moyle GJ. Better maintained adherence on switching from twice-daily to once-daily therapy for HIV: a 24-week randomized trial of treatment simplification using stavudine prolonged-release capsules. *HIV Med.* 2005;6:185-190.
15. Thiboutot D, Thieroff-Ekerdt R, Graupe K. Efficacy and safety of azelaic acid (15%) gel as a new treatment for papulopustular rosacea: results from two vehicle-controlled, randomized phase III studies. *J Am Acad Dermatol.* 2003;48:836-845.
16. Elewski BE, Fleischer AB Jr, Pariser DM. A comparison of 15% azelaic acid gel and 0.75% metronidazole gel in the topical treatment of papulopustular rosacea: results of a randomized trial. *Arch Dermatol.* 2003;139:1444-1450.
17. Zaghloul SS, Goodfield MJ. Objective assessment of compliance with psoriasis treatment. *Arch Dermatol.* 2004;140:408-414.
18. Jobling RG. Psoriasis—a preliminary questionnaire study of sufferers' subjective experience. *Clin Exp Dermatol.* 1976;1:233-236.
19. Serup J, Lindblad AK, Maroti M, et al. To follow or not to follow dermatological treatment—a review of the literature. *Acta Derm Venereol.* 2006;86:193-197.
20. Lee IA, Maibach HI. Pharmionics in dermatology: a review of topical medication adherence. *Am J Clin Dermatol.* 2006;7:231-236.

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