

# Azelaic Acid in the Treatment of Papulopustular Rosacea

## A Systematic Review of Randomized Controlled Trials

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**Objective:** To evaluate the clinical efficacy of topical 20% azelaic acid cream and 15% azelaic acid gel compared with their respective vehicles and metronidazole gel in the treatment of papulopustular rosacea.

**Data Sources:** Electronic searches of MEDLINE, EMBASE, BIOSIS, and SciSearch through July or August 2004 and the Cochrane Central Register of Controlled Trials through 2004 (issue 3). We performed hand searches of reference lists, conference proceedings, and clinical trial databases. Experts in rosacea and azelaic acid were contacted.

**Study Selection:** Randomized controlled trials involving topical azelaic acid (cream or gel) for the treatment of rosacea compared with placebo or other topical treatments. Two authors independently examined the studies identified by the searches. Ten studies were identified, of which 5 were included (873 patients).

**Data Extraction:** Two authors independently extracted data from the included studies, then jointly assessed methodological quality using a quality assessment scale.

**Data Synthesis:** Because standard deviation data were not available for 4 of the 5 studies, a meta-analysis could not be conducted. Four of the 5 studies demonstrated significant decreases in mean inflammatory lesion count and erythema severity after treatment with azelaic acid compared with vehicle. None of the studies showed any significant decrease in telangiectasia severity.

**Conclusions:** Azelaic acid in 20% cream and 15% gel formulations appears to be effective in the treatment of papulopustular rosacea, particularly in regard to decreases in mean inflammatory lesion count and erythema severity. Compared with metronidazole, azelaic acid appears to be an equally effective, if not better, treatment option.

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**R**OSACEA IS A COMMON DISORDER of the facial skin that affects an estimated 14 million Americans. Because of its effects on personal appearance, it can cause significant psychological, social, and occupational problems if left untreated. In recent surveys by the National Rosacea Society,<sup>1</sup> nearly 70% of patients with rosacea said this condition had lowered their self-confidence and self-esteem, and 41% reported that it had caused them to avoid public contact or cancel social engagements. Among those with severe symptoms, nearly 70% said the disorder had adversely affected their professional interactions, and nearly one third said they had even missed work because of their condition.

Rosacea is a chronic disorder affecting the skin and the eye. It is a syndrome of undetermined etiology characterized by vascular and papulopustular components mostly involving the face but occa-

sionally the neck and upper trunk. Clinical findings include midfacial erythema, telangiectasias, papules and pustules, and sebaceous gland hypertrophy. Rosacea is characterized by episodic flushing of affected areas, which may be associated with triggers such as consumption of alcohol, hot drinks, or spicy foods. During inflammatory episodes, affected areas of the skin develop papules, pustules, and swelling. Rhinophyma is a late finding. The skin lesions are notable for the absence of comedones, which helps to distinguish this disorder from acne vulgaris.

Rosacea occurs most commonly in adults aged 30 to 60 years. More than 10% of the general population in the United States exhibits dermatologic characteristics of rosacea.<sup>2</sup> Rare cases may also be found in children. Ocular involvement occurs in more than 50% of patients.<sup>3</sup> Skin involvement in rosacea is characterized by blotchy or diffuse erythema, telangiectasias, papules, pustules, and sebaceous gland

**Table 1. Search Terms\***

Term No.	MEDLINE, 1966 to August 2004	EMBASE, 1974 to August 2004
1	<i>Azelaic acid</i>	<i>Azelaic acid</i>
2	<i>Azelaic</i>	<i>Azelaic</i>
3	<i>Azelainic acid</i>	<i>Azelainic acid</i>
4	<i>Lepargylic acid</i>	<i>Lepargylic acid</i>
5	<i>Heptanedicarboxylic acid</i>	<i>Heptanedicarboxylic acid</i>
6	<i>Nonanedioic acid</i>	<i>Nonanedioic acid</i>
7	Azelex†	Azelex†
8	Finacea‡	Finacea‡
9	Finevin§	Finevin§
10	Skinoren	Skinoren
11	1, 2, 3, 4, 5, 6, 7, 8, 9, or 10	1, 2, 3, 4, 5, 6, 7, 8, 9, or 10
12	<i>Rosacea</i>	<i>Rosacea</i>
13	<i>Acne rosacea</i> [MeSH term]	<i>Rosacea</i>
14	<i>Rosacea</i>	12 or 13
15	<i>Erythema</i> [MeSH term]	11 or 14
16	<i>Flushing</i> [MeSH term]	
17	<i>Telangiectasia</i> [MeSH term]	
18	<i>Rhinophyma</i> [MeSH term]	
19	12, 13, 14, 15, 16, 17, or 18	
20	11 and 19	

Abbreviation: MeSH, Medical Subject Headings.

\*Search terms for BIOSIS, SciSearch, and the Cochrane Central Register of Controlled Trials included azelaic acid and rosacea; for Current Controlled Trials and ClinicalTrials.gov, azelaic acid.

†Indicates the proprietary formulation of 20% azelaic acid cream manufactured by Allergan Inc, Irvine, Calif.

‡Indicates the proprietary formulation of 15% azelaic acid gel manufactured by Berlex Laboratories Inc, Wayne, NJ (a US affiliate of Schering AG, Berlin, Germany), in conjunction with Allergan Inc.

§Indicates the proprietary formulation of 20% azelaic acid cream manufactured by Berlex Laboratories Inc in conjunction with Allergan Inc.

||Indicates the proprietary formulation of azelaic acid manufactured by Schering Health Care, West Sussex, England.

hypertrophy. The lesions tend to involve the nose, cheeks, chin, and central area of the forehead and may include the neck and chest. Initially, the hyperemia may be episodic, but after several months to years, it becomes chronic with the eventual development of telangiectasias. Rhinophyma, an irregular, lobulated thickening of the skin of the nose with follicular dilatation and a purplish red discoloration, may be a complication of long-standing involvement. Although the nose is the most common site of involvement, the cheeks, forehead, chin, or ears may also develop tissue hypertrophy. Subjective manifestations of rosacea are minimal, although some patients report a burning sensation during hyperemic episodes.

The cause of rosacea is poorly understood, although numerous theories have been offered. Hypotheses have included gastrointestinal, psychological, infectious, climatic, and immunological causes, although scientific evidence has not substantiated any of these as primary.<sup>4</sup> Prevalent current theories involve *Demodex folliculorum*. This organism feeds on sebum, and increased numbers of mites have been found on patients with rosacea.<sup>5</sup> Infection with *Helicobacter pylori* has also been proposed, and some reports show improvement of rosacea symptoms after eradication of this bacteria.<sup>6</sup> Climate, specifically exposure to extremes of sun and cold, may also affect the course of the disease, but the role is not clear.

Moderate to severe papulopustular rosacea may be treated with oral doses of tetracyclines, which are often effective, with improvement evident within 2 to 4 months after commencement of therapy. For mild to moderate involvement, topical treatment with metronidazole cream or gel applied to the affected areas twice daily has been successful.<sup>7</sup> More recently, studies have been performed with topical azelaic acid, a medication that has proven effective in the treatment of acne vulgaris.<sup>8</sup>

The exact mechanism of action of azelaic acid is not known. Azelaic acid has been shown to possess antimicrobial activity against *Propionibacterium acnes* and *Staphylococcus epidermidis*.<sup>9</sup> This antimicrobial action may be attributable to inhibition of microbial cellular protein synthesis. Electron microscopic and immunohistochemical evaluation of skin biopsy specimens from human subjects treated with azelaic acid cream demonstrated a reduction in the thickness of the stratum corneum, a reduction in the number and size of keratohyalin granules, and a reduction in the amount and distribution of filaggrin in epidermal layers.<sup>10</sup> Azelaic acid also possesses antityrosinase and antimitochondrial enzymatic activities. These may interrupt the hyperactivity of normal melanocytes and their resulting growth in melasma, a localized macular hyperpigmentation of facial or nuchal skin.<sup>11</sup> The hypopigmentation action of azelaic acid may result, to a lesser extent, from its ability to scavenge free radicals that can cause hyperactivity of melanocytes.

The aim of this review was to evaluate the clinical efficacy of topical 20% azelaic acid cream and 15% azelaic acid gel compared with their respective vehicles in the treatment of papulopustular rosacea.

## METHODS

### DATA SOURCES

A systematic search of the scientific literature from 1966 through July or August 2004 was conducted to identify all randomized controlled trials for topical azelaic acid for the treatment of rosacea compared with placebo or other topical treatments. Trials were identified by searches of MEDLINE (1966 to August 2004), EMBASE (1974 to August 2004), BIOSIS (1969 to July 2004), SciSearch (1990 to July 2004), the Cochrane Central Register of Controlled Trials (2004 [issue 3]), conference proceedings (American Academy of Dermatology and Society for Investigative Dermatology), and ongoing clinical trial databases (Current Controlled Trials [http://www.controlled-trials.com] and ClinicalTrials.gov [http://clinicaltrials.gov]). No language restrictions were applied. Studies that involved human or animal subjects were also included. Broad search terms were used to ensure that all potential studies involving azelaic acid for the treatment of rosacea were identified. The search terms are listed in **Table 1**. An alternate style for search terms is provided in **Table 2**.

The reference lists of all included studies and key review articles were searched to identify additional studies. At least 1 author from each of the 5 included studies was contacted to obtain data regarding standard deviation values of mean inflammatory lesion count before and after treatment with azelaic acid (cream or gel). Those authors and experts in the areas of rosacea and azelaic acid were consulted regarding their knowledge of further published and unpublished studies. A repre-

sentative from the manufacturer of azelaic acid 20% cream (Azelex; Allergan Inc, Irvine, Calif) was contacted for information regarding unpublished and published studies and ongoing trials. The same information was also requested from a dermatologist involved in the clinical development of dermatologic products at Berlex Laboratories Inc (Wayne, NJ), a US affiliate of Schering AG (Berlin, Germany) that produces 20% azelaic acid cream (Finevin) and 15% azelaic acid gel (Finacea) in conjunction with Allergan Inc.

## STUDY SELECTION

Based on the title and corresponding abstract obtained from the searches, studies were selected on the basis of the following inclusion criteria:

- All randomized controlled trials comparing the efficacy of topical 20% azelaic acid cream or 15% azelaic acid gel at any dose with vehicle control formulations in subjects with rosacea.
- Patients with a diagnosis of papulopustular rosacea, with no restrictions for sex or age.
- Primary outcome measure of physician-assessed changes in rosacea severity as determined by counts of inflammatory lesions (papules and pustules).
- Secondary outcome measures of physician- and/or device-assessed changes in rosacea severity, including severity of erythema and telangiectasia.

When it was uncertain whether a study met the inclusion criteria on the basis of the title and abstract alone, the entire article was reviewed. A study in Russian was translated by a Belarusian physician fluent in the language. Another study in German did not require translation because one of us (R.H.L.) could read the language. Two of us (R.H.L. and M.K.S.) conducted independent assessments of each study to determine their eligibility for inclusion in the review. Disagreements were resolved by discussion.

## DATA EXTRACTION

Data from eligible studies were independently extracted by 2 of us (R.H.L. and M.K.S.) using predeveloped forms. Details extracted from each study included the following:

- Study information: author(s), date of study, and study location.
- Study characteristics: study type (randomized controlled trial, matched control or unmatched concurrent control, or historic control), whether an a priori power calculation was performed, method of randomization of patients, and number and reason(s) for withdrawals.
- Patient characteristics: number of patients enrolled, age range (including mean age), sex, mean duration of rosacea, and inclusion and exclusion criteria.
- Intervention details: care setting, treatment group, control, cointerventions, duration of intervention, person who delivered the intervention, and whether the person who delivered the intervention, the care, and the patient were blinded.
- Outcome data: raw data on mean inflammatory lesion count, erythema severity, and telangiectasia severity; length of follow-up; and intervals at which outcome data were measured during follow-up.
- Analysis: description of analysis used and whether comparisons with active or vehicle controls were made.

Two of us (R.H.L. and M.K.S.) jointly used the quality assessment instrument for clinical trials developed by Jadad et al<sup>12</sup> to assess the methodological quality of the studies. Studies were given scores ranging from 0 (worst) to 8 (best) that were

**Table 2. Alternate Search Strategy\***

Term	MEDLINE and EMBASE
Rosacea	<i>Acne rosacea</i> [MeSH terms] OR <i>rosacea</i> [text word] OR <i>rhinophyma</i> [MeSH terms] OR <i>rhinophyma</i> [text word] OR <i>rosacea</i> [text word] OR <i>flushing</i> [MeSH terms] OR <i>flushing</i> [text word] OR <i>telangiectasia</i> [MeSH terms] OR <i>telangiectasia</i> [text word] OR <i>erythema</i> [MeSH terms] OR <i>erythema</i> [text word]
Azelaic acid	<i>Azelaic</i> [text word] OR <i>azelaic acid</i> [substance name] OR <i>azelaic acid</i> [text word] OR <i>heptanedecarboxylic acid</i> [text word] OR <i>lepargylic acid</i> [text word] OR <i>nonanedioic acid</i> [text word] OR <i>Finacea</i> † [text word] OR <i>Azelex</i> ‡ [text word] OR <i>Finevin</i> § [text word] OR <i>Skinoren</i>    [text word]

Abbreviation: MeSH, Medical Subject Headings.

\*Search terms for BIOSIS, SciSearch (Science Citation Index), Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov databases were *azelaic acid* and *rosacea*.

†Indicates the proprietary formulation of 15% azelaic acid gel manufactured by Berlex Laboratories Inc, Wayne, NJ (a US affiliate of Schering AG, Berlin, Germany), in conjunction with Allergan Inc, Irvine, Calif.

‡Indicates the proprietary formulation of 20% azelaic acid cream manufactured by Allergan Inc.

§Indicates the proprietary formulation of 20% azelaic acid cream manufactured by Berlex Laboratories Inc in conjunction with Allergan Inc.

||Indicates the proprietary formulation of azelaic acid manufactured by Schering Health Care, West Sussex, England.

based on the following guidelines: randomization, double blinding, and description of withdrawals and dropouts (**Table 3**).<sup>13-15</sup> Four studies had a score of 8, and 1 study had a score of 7.

## RESULTS

### DESCRIPTION OF STUDIES

Using the search strategy described in the preceding section, we identified 9 randomized controlled trials involving azelaic acid (20% cream or 15% gel formulations) in the treatment of rosacea. Of those trials, 2 studies compared topical azelaic acid with topical metronidazole and were therefore excluded from the review.<sup>16,17</sup> Two other publications were duplicate studies (Hebert<sup>18</sup> and Thiboutot et al<sup>19</sup>). The 5 remaining randomized controlled trials were included for systematic analysis (**Table 4**). One trial was conducted in Wales, and another was completed in Norway. The remaining 3 studies were conducted in the United States.

All 873 patients enrolled in the included studies, had evidence of papulopustular rosacea as assessed by a physician. Three studies were conducted in the 1990s, and 2 since 2000. The number of participants in the studies ranged from 33 to 335, with a greater proportion of female participants in most of the studies. The treatment groups in the included studies were comparable at baseline with regard to the mean number of facial inflammatory lesions and the severity of erythema and telangiectasia. The duration of the trials ranged from 9 weeks to 3 months. The trial by Carmichael et al<sup>14</sup> was a split-face comparison whereby patients applied azelaic acid cream to one half of the face and its identical-appearing vehicle to the other half. All other included studies in-

**Table 3. Quality Assessment Scores for 5 Studies Comparing Azelaic Acid vs Vehicle\***

Guideline	Source				
	Bjerke et al, <sup>13</sup> 1999	Carmichael et al, <sup>14</sup> 1993	Thiboutot et al, <sup>15</sup> 2003 (Study 1)	Thiboutot et al, <sup>15</sup> 2003 (Study 2)	Bamford et al, 1999†
Randomized	1	1	1	1	1
Appropriate randomization	1	1	1	1	1
Double-blind	1	1	1	1	1
Appropriate blinding (identical placebo)	1	1	1	1	1
Description of withdrawals/dropouts	1	1	1	1	1
Description of methods of statistical analysis	1	1	1	1	1
Clear description of inclusion/exclusion criteria	1	1	1	1	1
Description of method used to assess adverse effects	1	1	1	1	0
<b>Total Score</b>	<b>8</b>	<b>8</b>	<b>8</b>	<b>8</b>	<b>7</b>

\*Assessment scores are described in the "Data Extraction" subsection of the "Methods" section.

†Noel T. Bamford, MD, David E. Gargeness, PharmD, Colleen M. Reiner, Robert L. Tilden, DrPH, MPH, unpublished data, 1999.

volved separate groups of participants who were randomly assigned to receive azelaic acid or its identical-appearing vehicle. Application of azelaic acid or its vehicle was twice daily. Concomitant therapy that had the potential to influence the course of rosacea was specifically disallowed in all of the studies.

In addition to the primary outcome measure (mean number of inflammatory papules or pustules), all of the studies assessed other outcome measures such as the severity of erythema and telangiectasia. Because there are currently no standardized methods for evaluating papulopustular rosacea, there was great variability in the scoring of erythema intensity and telangiectasia (Table 4).<sup>13-15</sup>

In all studies except one (Noel T. Bamford, MD, David E. Gargeness, PharmD, Colleen M. Reiner, Robert L. Tilden, DrPH, MPH, unpublished data, 1999), participants who were treated with azelaic acid cream or gel experienced significant reductions in mean inflammatory lesion counts compared with those treated with the respective vehicles ( $P < .05$ ) (Table 4).<sup>13-15</sup> The study by Bamford et al showed significant reductions in the group treated with 20% azelaic acid cream and the control group (49% and 28%, respectively), with no significant difference in reduction between the groups. Although the included studies used some form of statistical test to evaluate the data, the standard deviation and/or standard error of continuous measurements were not available in any of the studies except for the unpublished study by Bamford et al. Despite the variability of ratings for erythema severity, there was an overall greater reduction in erythema severity in patients who used azelaic acid vs vehicle in 4 of the 5 studies (Table 4). The unpublished study by Bamford et al showed equal improvement in erythema severity for both the azelaic acid and control groups (32%). There was no significant improvement in telangiectasia severity noted among patients using azelaic acid or vehicle in any of the included studies. Compared with the vehicle, common treatment-related adverse effects associated with azelaic acid use consisted of local cutaneous irritation symptoms such as burning and stinging. In most cases, the symptoms were transient and mild to moderate in intensity.

### LIMITATIONS OF THIS STUDY

This review had several limitations. Because the standard deviations of mean inflammatory lesion counts before and after treatment with 20% azelaic acid cream or 15% azelaic acid gel could not be obtained from most of the included studies, a meta-analysis could not be performed. Because standardized methods for evaluating the severity of erythema and telangiectasia in papulopustular rosacea do not currently exist, it could only be generalized that azelaic acid cream or gel reduces erythema and has minimal effect on telangiectasia. Ideally, a system similar to the Psoriasis Area and Severity Index should be developed to evaluate rosacea severity (number of inflammatory lesions and severity of erythema and telangiectasia). Thiboutot et al<sup>19</sup> have developed a novel 7-point static investigator's global assessment scale that appears to be a promising evaluation system for rosacea.

Future studies should include standard deviations for data such as inflammatory lesion count to allow for objective comparisons of efficacy between azelaic acid and control treatments.

### COMMENT

Azelaic acid has been shown to be effective in the treatment of acne vulgaris. In recent years, it has emerged as a potentially effective medication for treating the papulopustular form of rosacea. This systematic review sought to evaluate the clinical efficacy of topical 20% azelaic acid cream and 15% azelaic acid gel compared with their respective vehicles in the treatment of papulopustular rosacea.

The results of our review demonstrate that patients with papulopustular rosacea appear to derive substantial benefit with regard to decreased mean inflammatory lesion count when treated with azelaic acid cream or gel.

Azelaic acid has also been shown to be as effective as, if not better than, topical metronidazole, a standard of

**Table 4. Study Characteristics for 7 Studies Comparing Topical AZA vs Veh or Metro**

Characteristic	Source						
	Bjerke et al, <sup>13</sup> 1999	Carmichael et al, <sup>14</sup> 1993	Thiboutot et al, <sup>15</sup> 2003 (Study 1)	Thiboutot et al, <sup>15</sup> 2003 (Study 2)	Bamford et al, 1999*	Elewski et al, <sup>16</sup> 2003	Maddin, <sup>17</sup> 1999
No. of patients (No. in treatment groups)	114 (76 AZA vs 38 Veh)	33	329 (164 AZA vs 165 Veh)	335 (169 AZA vs 166 Veh)	53 (27 AZA vs 26 Veh)	251 (124 AZA vs 127 Metro)	40
Intervention treatment	20% AZA cream	20% AZA cream	15% AZA gel	15% AZA gel	20% AZA cream	15% AZA gel	20% AZA cream
Control treatment	Veh	Veh	Veh	Veh	Veh	0.75% Metro gel	0.75% Metro cream
Duration of trial	3 mo	9 wk	12 wk	12 wk	9 wk	15 wk	15 wk
Method of intervention	2 Treatment groups	Contralateral split-face comparison	2 Treatment groups	2 Treatment groups	2 Treatment groups	2 Treatment groups	Contralateral split-face comparison
Dropout rates, %	18.1	0	14.0 Overall; 19 AZA vs 9 Veh	11.6 Overall; 11 AZA vs 12 Veh	6.7 Overall; 5 AZA vs 1.7 Veh	11.3 AZA vs 7.9 Metro	7.5
Mean No. of inflammatory lesions†							
Before/after AZA treatment	30.8/8.3	14.2/2.5	17.5/6.8	17.8/8.9	16.2/8.3	18.1/4.5	11.30/2.43
Before/after control treatment	31.7/15.3	15.0/6.6	17.6/10.5	18.5/12.1	13.4/9.1	19.4/7.6	11.40/3.49
Change, AZA vs control treatment							
Erythema	Mean reduction in erythema severity score, 47.9% vs 37.9% (P = .03)	Reduction in mean erythema index (calculated), 7.2% vs 2.8% (P = .04)	Improvement in 44% vs 29% of patients (P = .002)	Improvement in 46% vs 28% of patients (P < .001)	Improvement in erythema, 32% vs 32%	Improvement in erythema severity in 56% vs 42% of patients (P = .02, reduction in overall facial erythema)	Reduction in mean erythema score, 25.5% vs 18.7% (P = .07)
Telangiectasia	Mean reduction in telangiectasia score, 22.3% vs 23.5% (P = .98)	Change in telangiectasia score (calculated), 2.3% decrease vs 2.2% increase	Unchanged in 77% vs 80% of patients	Unchanged in 73% vs 78% of patients	Improvement in 46.2% of patients vs increase in 27.3%	Unchanged in 73% vs 76% of patients	No significant effect (no specific data values provided)
Scoring systems for erythema and telangiectasia severity	Degree on 7-digit scale (0, none; 6, severe)	Erythema index using an erythema meter; degree of telangiectasia on 10-point visual analog scale scoring system and an electronic meter	Erythema severity 4-digit scale (0, none; 3, severe); telangiectasia severity rated none, mild, moderate, or severe	Same as Thiboutot et al, <sup>15</sup> study 1	Erythema and telangiectasia severity rated as 0 (no involvement), 1 (mild/moderate, 1%-49% of skin area), or 2 (severe, 50%-100% of skin area)	Erythema and telangiectasia severity 4-point scale (0, none; 3, severe)	Erythema and telangiectasia severity 4-digit scale (1, none; 4, severe or marked)

Abbreviations: AZA, azelaic acid; Metro, metronidazole; Veh, vehicle.

\*Noel T. Bamford, MD, David E. Gargenese, PharmD, Colleen M. Reiner, Robert L. Tilden, DrPH, MPH, unpublished data, 1999.

†Inflammatory lesions are identified as papules and pustules.

treatment for papulopustular rosacea. In 1999, Maddin<sup>17</sup> conducted a single-center, randomized, double-blind study comparing topical 20% azelaic acid cream and topical 0.75% metronidazole cream. Both treatment groups experienced significant decreases in inflammatory lesion counts (mean number of lesions, 11.30 at baseline vs 2.43 after treatment for azelaic acid and 11.40 vs 3.49 for metronidazole;  $P = .43$ ), although no statistically significant difference was observed between the 2 treatment groups. In a randomized, double-blind, parallel-group study conducted by Elewski et al<sup>16</sup> in 2003, patients who received 15% azelaic acid gel demonstrated a significantly greater mean decrease in inflammatory lesion count (baseline to last visit at week 15) compared with those who received 0.75% metronidazole gel ( $P = .003$ ). In addition, there was a greater reduction in overall facial erythema in the azelaic acid group ( $P = .02$ ). The studies by Maddin<sup>17</sup> and Elewski et al<sup>16</sup> demonstrated no significant improvement in telangiectasia se-

verity for the azelaic acid or the metronidazole group (Table 4). Although patients experienced minor local skin irritation with use of azelaic acid compared with metronidazole, local tolerability was high. The study by Maddin<sup>17</sup> showed that although patients experienced trace stinging with application of azelaic acid cream, a significantly greater number of those patients preferred to use azelaic acid again compared with metronidazole cream (92% vs 66%;  $P = .005$ ). The study by Elewski et al<sup>16</sup> demonstrated that 89% of patients in the azelaic acid gel group rated their treatment as "good or acceptable despite minor irritation" vs 96% of patients in the metronidazole gel group.

The use of 20% azelaic acid cream or 15% azelaic acid gel appears to be effective in the treatment of papulopustular rosacea, particularly in regard to decreases in mean inflammatory lesion count and severity of erythema. Compared with metronidazole, azelaic acid appears to be an equally effective, if not better, treatment option.

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## Announcement

Free color publication if color illustrations enhance the didactic value of the article.