

Acne Vulgaris: The Majority of Patients Do Not Achieve Success According to FDA Guidance

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ABSTRACT

Background: The Food and Drug Administration (FDA) recommends grading acne vulgaris via an Investigator's Global Assessment (IGA) scale and assessing treatment as either success or failure, with success defined as clear (grade 0) or almost clear (grade 1) with at least a two-grade improvement in acne severity from baseline.
Objective: To determine the likelihood of achieving real world treatment success in patients with acne according to FDA guidance.
Methods: We calculated estimated appropriates to obtain the IGA 0/1 (clear or almost clear rate) for many of the oral and topical medications. We also used the National Ambulatory Medical Care Survey (NAMCS) data to determine the number of medications prescribed for outpatient visits when isotretinoin was prescribed or when isotretinoin was not prescribed and the one and only diagnosis was acne.
Results: Isotretinoin had the highest IGA 0/1 at 87%. None of the other medications had an IGA 0/1 > 40%. Of all outpatient acne visits, only 6% receive isotretinoin. When excluding isotretinoin visits, 71% of patients received ≤ 2 medications.
Limitations: The majority of the acne medication studies lasted 12 weeks, however, it can take 6 months or longer to get the maximum effect. None of the studies combined topical and oral medications.
Conclusions: The majority of acne patients are not likely to achieve success according to FDA guidance. We propose that the FDA guidance may be too rigorous. An alternative hypothesis is that most acne patients are undertreated.

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INTRODUCTION

Acne vulgaris is a common inflammatory skin condition that affects approximately 85% of teenagers at some point in their lives and up to 20% may develop facial scarring.[1,2] Although acne primarily affects younger individuals, acne can persist into adulthood and can affect any age group. Acne can lead to severe scarring and psychological distress leading to lower self-esteem, anxiety, and depression.[3] There are many different treatments for acne and many providers will choose a treatment regimen based on the clinical type (comedonal, papulopustular, mixed, or nodular) and severity.[1]

There are many different scales for grading acne severity. FDA recommends grading acne via an IGA scale. The different grades include clear (grade 0), almost clear (grade 1), mild severity (grade 2), moderate severity (grade 3), and severe (grade 4).[4] The FDA suggests assessing treatment as either success or failure, with success defined as clear (grade 0) or almost clear (grade 1) with at least a two-grade improvement in acne severity from baseline.[4]

The purpose of this study is to determine the likelihood of success in patients with acne according to FDA guidance. Since first-line treatment for acne can include combination therapy, we will also determine the number of medications prescribed in acne outpatient visits.

MATERIALS AND METHODS

Clear or Almost Clear Rate for Medications in Acne

In this retrospective study, we relied on the FDA highlights of prescribing information to obtain the IGA 0/1 for all of the topical medications and two of the oral medications, sarecycline and drospirenone-ethinyl estradiol. For the remaining oral medications, we searched peer-reviewed publications to obtain the clear or almost clear rate. If there were multiple studies for a medication, we calculated an appropriate weighted estimate. All of the studies identified 12 weeks, except for the isotretinoin studies, which lasted 20 weeks and the drospirenone-ethinyl estradiol studies, which lasted 24 weeks.

The FDA suggests grading acne outcomes via an IGA scale, however, a few of the studies included other scoring scales such as the Evaluator's Global Severity (EGS) or the Global Acne Assessment Score (GAAS). For the purposes of this paper, we can assume that the other scoring scales were equivalent to the

IGA. According to FDA guidance, success was defined as IGA 0/1 with at least a two-grade improvement in acne severity from baseline.[4]

Number of Medications Prescribed in Acne Visits

Data from the 2012 to 2016 NAMCS was used to determine the number of medications prescribed for outpatient visits when isotretinoin was prescribed or when isotretinoin was not prescribed and the one and only diagnosis was acne.[5] These surveys were developed and implemented by the National Center of Health Statistics, part of the Center for Disease Control and Prevention (CDC). Results from the survey provide nationally representative yearly estimates of non-hospital-based outpatient healthcare utilization.[5] To account for the variance caused by the complex survey design, and for all analyses we used survey weights to provide the more precise estimates. In order to maximize the likelihood that we would be examining visits exclusively for the treatment of acne, we limited the analysis to those visits with one and only one diagnosis.

Reduction in Lesions vs Clear or Almost Clear Rate

The FDA recommends assessing the number of inflammatory and non-inflammatory lesions before and after treatment. We relied mainly on the FDA highlights of prescribing information to obtain the percentage reduction in inflammatory and non-inflammatory lesions. If there were multiple studies, we created estimated appropriates for the percentage reduction.

We performed two separate linear regression analyses, one comparing the percentage reduction in inflammatory lesions to the percentage achieving IGA 0/1, and a second analysis comparing the percentage reduction in non-inflammatory lesions to the percentage achieving IGA 0/1.

RESULTS

Clear or Almost Clear Rate for Medications in Acne

According to the FDA highlights of prescribing information, IGA 0/1 of topical medications ranged from 16% to 38% at the end of 12 weeks (Table 1).[6–16] Dapsone gel 5% had the highest IGA 0/1 rate at 38%,[8] whereas adapalene gel 0.1% had the lowest IGA 0/1 rate at 16% (see table 1).[6] Increasing the strength of adapalene gel to 0.3% resulted in a 5% increase in the IGA 0/1 (see Table 1).[6] Combining two medications together was more successful in achieving IGA 0/1 than either medication alone. For example, adapalene gel 0.1% had an IGA 0/1 of 16% and when adapalene gel 0.1% was combined with benzoyl peroxide gel 2.5%, the IGA 0/1 increased to 32% (see Table 1).[10] However, the success rate of the medications was not additive. For example, benzoyl peroxide gel 2.5% had an IGA 0/1 of 21%; clindamycin gel 1.2% had an IGA 0/1 rate of 22%; and clindamycin phosphate and benzoyl peroxide gel 1.2%/2.5% had an IGA 0/1 rate of 29% (see Table 1).[10]

TABLE 1.

Topical Drug Efficacy in Acne Vulgaris

Drug	Clear or Almost Clear (IGA 0/1) at 12 Weeks	Number of Agents
Adapalene gel 0.1%[6]	16%	1
Tretinoin lotion 0.05%[7]	18%	1
Tazarotene cream 0.1%[9]	19%	1
Adapalene gel 0.3%[6]	21%	1
Benzoyl Peroxide gel 2.5%[10]	21%	1
Clindamycin gel 1.2%[10]	22%	1
Minocycline foam 4%[11]	22%	1
Clindamycin phosphate and benzoyl peroxide gel 1.2%/2.5%[10]	29%	2
Tazarotene foam 0.1%[12]	29%	1
Dapsone gel 7.5%[13]	30%	1
Adapalene and benzoyl peroxide gel 0.1%/2.5%[14]	32%	2
Clindamycin phosphate and tretinoin gel 1.2%/ 0.025%[15]	32%	2
Trifarotene cream[16]	36%	1
Dapsone gel 5%*[8]	38%	1

*Dapsone gel 5% was applied twice daily, whereas Dapsone gel 7.5% was applied once daily

TABLE 2.

Oral Drug Efficacy in Treating Acne Vulgaris

Drug	Clear or Almost Clear (IGA 0/1)	Number of Agents
Extended release minocycline[19]	17%	1
Drospirenone/ethinyl estradiol tablet[21]	18%	2
Sarecycline tablet[20]	22%	1
Doxycycline calcium tablet[18]	30%	1
Isotretinoin capsule[17]	87%	1

For the oral medications, isotretinoin had by far the highest IGA 0/1 at 87%,[17] and the second highest rate was that of doxycycline at 30% (Table 2).[18] Extended release minocycline had an IGA 0/1 of 17%, which was the lowest amongst the oral medications (see Table 2).[19] Isotretinoin was the only medication to have an IGA 0/1 >40%.

Number of Medications Prescribed in Acne Visits

According to the NAMCS data from 2012-2016, there were a total of 3,307 outpatient visits where acne was the one and only diagnosis, estimating the experience of 72.7 million (95% CI: 70.1, 74.8) outpatient visits. Of these, 4.6 million (3.8, 5.4) visits, representing 6.4% (5.3, 7.5) of these acne visits, were isotretinoin-treated patients.

TABLE 3.

National Ambulatory Medical Care Survey Estimates from 2012 to 2016: Number of Medications Prescribed for Acne Management (Excluding Isotretinoin Patients)

Number of Medications	Number of Medications	Proportion of Total Visits (95% Confidence Interval)
0	4.6 (3.7,5.4)	6.7 (5.5, 7.9)
1	21.8 (20.2, 23.5)	32.0 (29.9, 34.2)
2	21.8 (20.2, 23.4)	32.0 (29.9, 34.1)
3	14.0 (12.8, 15.3)	20.6 (18.8, 22.4)
≥ 4	5.9 (4.4, 7.5)	8.7 (6.5, 11.0)

FIGURE 1. Reduction in inflammatory lesions vs clear or almost clear rate. There is a significant relationship between the percentage reduction in inflammatory lesions and IGA 0/1(R^2=0.3, *P*=0.03).

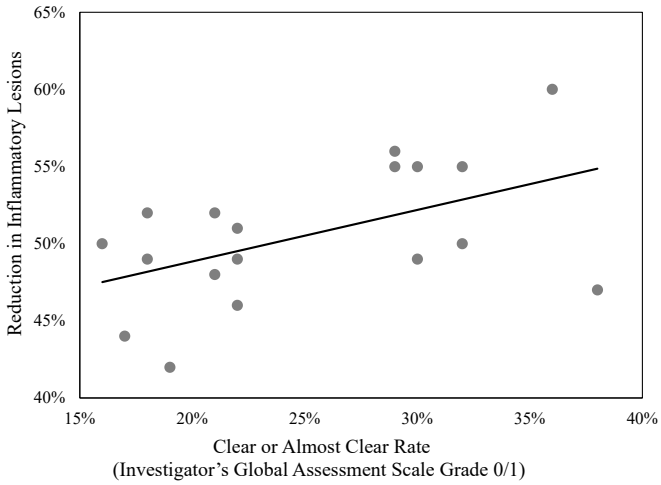
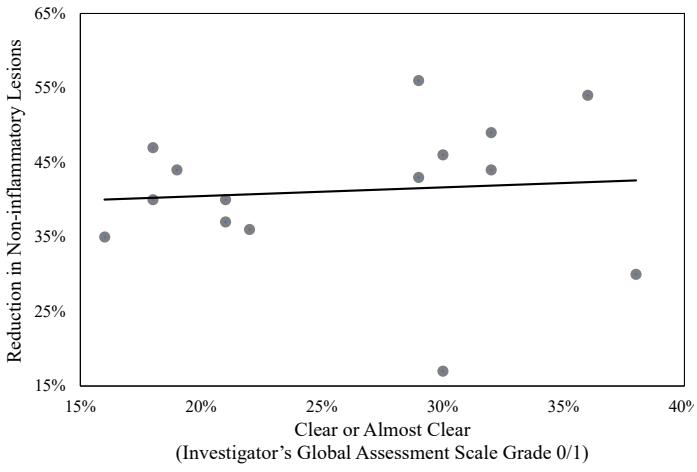


FIGURE 2. Reduction in non-inflammatory lesions vs clear or almost clear rate. There is no significant relationship between the percentage reduction in non-inflammatory lesions and IGA 0/1 (R^2=0.007, *P*=0.8).



For the rest of the 68.1 million visits in which isotretinoin was not prescribed, we determined the number of medications prescribed. 48.1 million (44.1, 52.2) visits resulted in either 0, 1, or 2 medications being prescribed, whereas 19.9 million (17.2, 22.7) visits resulted in 3 or more medications (see Table 3). The majority of patients received either 0, 1, or 2 medications: 70.7% (65.2, 76.2).

Reduction in Lesions vs Clear or Almost Clear Rate

According to the FDA highlights of prescribing information, the percentage in inflammatory lesion reduction ranged from 42% to 60% and the percentage in non-inflammatory lesion reduction ranged from 17% to 56% (Figures 1 and 2).[6–16,18–21] For the linear regression analysis comparing the percentage reduction in inflammatory lesions to the percentage achieving IGA 0/1, the relationship was significant (R^2=0.3, *P*=0.03) (see Figure 1). For the linear regression analysis comparing the percentage reduction in non-inflammatory lesions to the percentage achieving IGA 0/1, the relationship was not significant (R^2=0.007, *P*=0.8) (see Figure 2).

DISCUSSION

Isotretinoin had the highest IGA 0/1 at 87%. None of the other drugs had an IGA 0/1 >40%. For most outpatient acne visits, isotretinoin is not prescribed (94%) and the majority of these patients receive 0, 1, or 2 medications (71%). Based on these findings, the majority of acne patients are not achieving success according to FDA guidance. Since FDA success must also include a two-grade improvement, the true success rate will be lower than the IGA 0/1 rate. Rather than conclude that most providers are prescribing medication regimens that result in failure, we believe that the FDA guidance may be too conservative.

We propose that further studies assess the relationship between reduction in both inflammatory and non-inflammatory lesions and IGA 0/1 as this may help develop alternative definitions of success in acne treatment. For example, the Hidradenitis Suppurativa Clinical Response (HiSCR) is a valid and meaningful endpoint for hidradenitis suppurativa.[22] HiSCR defines success as >50% reduction in inflammatory lesion count with no increase in abscesses or draining fistulas.[22]

Regulatory agencies require improvement on outcomes by assessment of both investigators and subjects. We were unable to find any studies comparing patient assessment of disease improvement or patient assessment of disease-specific quality of life to IGA 0/1, and further studies on this topic may help redefine acne treatment success.

There are several limitations to this study. None of the studies combined oral and topical medications, and there is a possibility that combining oral and topical medications may significantly increase the likelihood of success. None of the studies included 3 or more medications, and it is possible that using 3 or more

medications may increase the IGA 0/1 to >50%. Also, the majority of the acne medication studies lasted 12 weeks, however, it can take 6 months or longer to get the maximum effect. Another limitation is that most of the studies excluded patients with mild acne, so extrapolation of this population is not possible in our database.

Taken altogether, this study demonstrates that the majority of physician-treated acne patients in the United States are not likely to achieve success according to FDA guidance.

Further studies should be done to demonstrate a clinically meaningful severity difference, or minimum clinically important difference, in acne severity and these studies may help redefine acne treatment success.

DISCLOSURES

Dr. Fleischer is an investigator for Galderma and Trevi and is a consultant for Boehringer Ingelheim, Incyte, Qurient, Syneos. Keshav and Dr. Baquerizo Nole do not have any disclosures to report.

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