Fixed-Dose Combination Gel of Adapalene and Benzoyl Peroxide plus Doxycycline 100 mg versus Oral Isotretinoin for the Treatment of Severe Acne: Efficacy and Cost Analysis

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Background: Acne vulgaris is a chronic skin disease with a high prevalence. Left untreated or inadequately treated, acne vulgaris can lead to psychological and physical scarring, as well as to unnecessary medical expenses. Oral isotretinoin is an effective treatment for severe resistant nodular and conglobate acne vulgaris. A regimen consisting of a fixed-dose combination of adapalene and benzoyl peroxide gel, 0.1%/2.5% (A-BPO) with oral doxycycline 100 mg (A-BPO/D) has been demonstrated to be efficacious and well tolerated in patients with severe acne and may be an alternative to oral isotretinoin for some patients with severe acne.

Objective: The objective of this analysis was to compare the relative efficacy and associated costs of A-BPO/D versus oral isotretinoin.

Methods: In this analysis, comparisons of relative efficacy were made using previously published studies involving similar patient populations with severe acne that warrant the use of oral isotretinoin. The pricing for oral doxycycline and oral isotretinoin was estimated based on the maximum allowable cost from 9 states, and the pricing for A-BPO was calculated as the range between the average wholesale price and the wholesale acquisition cost. For this analysis, 2 treatment models were generated to compare costs: (1) a basic treatment model that examined the costs of an initial regimen of either A-BPO/D or oral isotretinoin without considering probable outcomes, and (2) a long-term model that factored in likely treatment outcomes and subsequent treatments into associated costs. The basic treatment model assumed that patients would be prescribed a single regimen of A-BPO/D for 12 weeks or oral isotretinoin for 20 weeks. The long-term model considered the probability of each treatment successfully managing patients’ acne, as well as likely additional regimens of A-BPO monotherapy or an additional regimen of oral isotretinoin. As a result of different treatment durations, the costs for each treatment were normalized to weekly cost of treatment.

Results: Based on evidence from the published literature, patients treated with A-BPO/D would be expected to have an initial 72% reduction in inflammatory lesions, and patients treated with oral isotretinoin would have an 80% to 90% reduction of these lesions. The median weekly cost for the basic treatment model was $44 for A-BPO/D and $62 for oral isotretinoin. The weekly median costs for the long-term model were $44 for patients initially receiving a regimen of A-BPO/D followed by a maintenance regimen of A-BPO monotherapy and $50 for patients receiving an initial regimen of A-BPO/D who required a subsequent regimen of oral isotretinoin. The weekly cost for oral isotretinoin in the long-term model was $62.

Conclusions: The comparison of these 2 treatments demonstrated that they are both effective in treating severe acne, and that A-BPO/D was less expensive weekly than oral isotretinoin. These models show that A-BPO/D is safer than and is a more cost-effective alternative to oral isotretinoin for treating patients with severe acne vulgaris.
Acne vulgaris is a chronic, prevalent skin disease that can affect a patient's quality of life and lead to unnecessary medical expenses. Oral isotretinoin is indicated for the treatment of severe resistant nodular and conglobate acne vulgaris and is the only therapy that targets all 4 causative factors. However, oral isotretinoin is a teratogenic drug that is associated with significant side effects and carries a REMS program; and although it is indicated for severe recalcitrant acne, it is often prescribed for mild or moderate acne.

A fixed-dose combination of adapalene and benzoyl peroxide gel, 0.1%/2.5% (A-BPO) is efficacious and well tolerated in patients with severe acne. This new analysis of previously published data shows that although oral isotretinoin and A-BPO plus oral doxycycline 100 mg (A-BPO/D) are both effective for treating severe acne, A-BPO/D is less expensive per patient per week. Because the 2 treatment regimens are different in nature, a weekly cost analysis was used for comparison, showing that the median weekly cost for A-BPO/D is $44 compared with $62 for oral isotretinoin.

In addition to being safer than oral isotretinoin for the management of patients with severe acne vulgaris, A-BPO/D is a cost-effective alternative to oral isotretinoin, which is associated with potential serious side effects that may further increase the indirect costs of treatment.

The pathophysiology of acne is multifactorial, involving 4 causative factors, including inflammation, hyperkeratinization, Propionibacterium acnes proliferation, and excess sebum production. Several topical and oral treatment options target the various causative mechanisms. The Global Alliance to Improve Outcomes in Acne has published recommended guidelines for the treatment of acne. Topical treatment is recommended for milder forms of acne. Oral isotretinoin is indicated for the most severe forms of nodular and conglobate acne and is the only available therapy that targets all 4 causative factors.

Although indicated for severe recalcitrant acne, oral isotretinoin is frequently prescribed for the treatment of mild or moderate acne. However, oral isotretinoin is a pregnancy category X teratogen and is associated with significant side effects. The reported side effects associated with the use of oral isotretinoin include depression, attempted suicide, cheilitis, dermatitis, myalgia, dry eyes, nonspecific gastrointestinal symptoms, and arthralgia, among others. Patients who are prescribed oral isotretinoin must enroll in the Risk Evaluation and Mitigation Strategy (REMS) program iPLEDGE. Patients also require laboratory tests to monitor liver function and serum lipid levels.

For patients with severe acne with less nodular involvement, an oral antibiotic with a topical retinoid and benzoyl peroxide is recommended. Doxycycline 100 mg once daily is efficacious against acne and is relatively well tolerated. Adapalene, a third-generation retinoid with an established safety profile, has antimicrobial and anti-inflammatory properties that are effective against acne. Benzoyl peroxide is an antimicrobial agent with demonstrated efficacy in treating acne. Benzoyl peroxide is more advantageous than other topical antibiotics, because it does not induce bacterial resistance and because it is effective against resistant P. acnes strains.

A fixed-dose combination of adapalene and benzoyl peroxide gel, 0.1%/2.5% (A-BPO; Epiduo Gel) was approved by the US Food and Drug Administration in 2008. This is the only fixed-dose drug combination that is formulated with a topical retinoid and benzoyl peroxide. The safety and efficacy of A-BPO for the treatment of acne have been established in clinical trials.

Two related clinical trials investigated the use of A-BPO with oral doxycycline 100 mg once daily (A-BPO/D) for 12 weeks, followed by a maintenance therapy of A-BPO in patients with severe acne for an additional 24 weeks. Severe acne vulgaris in these studies was defined as up to 3 nodules or cysts, 30 to 120 noninflammatory lesions, and at least 20 inflammatory lesions. In the study by Gold and colleagues, patients who were treated with A-BPO/D had significantly better improvement in acne symptoms and in the acne symptom portion of the Acne-QOL questionnaire than patients given vehicle gel and doxycycline 100 mg. Patients with at least a “good” improvement in the first study, whether they were in the A-BPO/D group or in the vehicle gel plus doxycycline group, were eligible for the second study and were randomized to a maintenance regimen of A-BPO or to vehicle gel. Symptoms of acne and the QOL of patients using A-BPO continued to improve, whereas in patients using vehicle gel, QOL and
acne symptoms worsened during the 24-week period.\textsuperscript{9,27} The majority of adverse events were mild and included erythema, scaling, dryness, and stinging and burning.\textsuperscript{25,27}

In addition to treating severe acne, A-BPO is also recommended for the treatment of mild and moderate acne, making it a versatile topical medication that can treat a spectrum of disease severity.\textsuperscript{12}

A model was developed to compare the efficacy and related costs of A-BPO/D versus oral isotretinoin in treating severe acne vulgaris.

**Methods**

**Efficacy**

Efficacy estimates used for the present comparison were based on the percent in reduction of inflammatory lesions from previously reported data.\textsuperscript{26-30} These data were pulled from independent studies with different study populations. However, all patients in these studies had severe acne, for which a specialist would likely prescribe oral isotretinoin.

Efficacy data for oral isotretinoin were pulled from 3 clinical studies using different doses\textsuperscript{26-30} so that an accurate range of the drug’s efficacy could be calculated and used for this analysis rather than selecting an individual study for our comparison.

The treatment period for A-BPO/D is 12 weeks and for oral isotretinoin it is 20 weeks. Therefore, comparisons of efficacy were made between A-BPO/D and oral isotretinoin after 12 weeks and 20 weeks of treatment, respectively. However, because the treatment regimens are different, the percent reduction in lesions was also determined after 20 weeks for A-BPO/D by combining the 12 weeks of A-BPO/D treatment with the 8 subsequent weeks of A-BPO maintenance therapy. This additional efficacy measurement was determined to facilitate a relative comparison between A-BPO/D and oral isotretinoin after 20 weeks of treatment.

**Pricing**

Pricing for oral doxycycline and oral isotretinoin was estimated from the maximum allowable cost from 9 states, including Texas, Illinois, New York, Pennsylvania, New Jersey, Michigan, Georgia, Iowa, and Wyoming. The maximum allowable cost pricing data were downloaded from these states’ respective Medicaid agencies on June 7, 2012, and May 15, 2012, for oral doxycycline (100 mg) and for oral isotretinoin (10-40 mg), respectively. Currently only generic forms of oral isotretinoin are available in the United States. Maximum allowable cost pricing was unavailable for A-BPO.

Pricing was set to be the range between the average wholesale price (AWP) and the wholesale acquisition cost (WAC). Because the duration of treatment differs between the 2 regimens, pricing was calculated as cost per week of treatment.

**Treatment Models**

Two treatment models were generated. The basic treatment model examined the cost of drugs in the treatment regimen of A-BPO/D or of oral isotretinoin and did not take into account the likely outcomes or costs of the follow-up treatments. A long-term treatment model was developed that factored in likely treatment outcomes and subsequent treatments. This model also considered in the cost of drugs the probability that a certain treatment would be required.

**Basic treatment model.** A basic decision tree was constructed in which patients could only receive either a regimen of A-BPO/D for 12 weeks or a regimen of oral isotretinoin for 20 weeks. Two tubes of A-BPO were distributed to patients during the 12-week regimen; the second tube was given between weeks 8 and 12 to ensure that patients had sufficient study drug to complete the 12-week regimen (unpublished data). Therefore, it was assumed that 2 tubes of A-BPO would be distributed in a 12-week period. It was also assumed that 1 dose of doxycycline or oral isotretinoin would be used daily during the treatment period. The weekly cost of treatment for both regimens was then calculated and compared, using the pricing details previously described.

**Long-term treatment model.** This latter decision tree begins with an initial 12-week treatment with A-BPO/D or a 20-week treatment with oral isotretinoin. The long-term treatment model considered the probability of each treatment being successful in managing acne. This model did not assess likely reductions in acne lesions. The percentages of patients with symptoms under control or those with relapsed disease were obtained from previously published data.\textsuperscript{26,27,14} The long-term treatment model assumed that patients whose symptoms were not controlled or whose disease relapsed, regardless of the initial treatment regimen, would receive a 20-week regimen of oral isotretinoin.

All patients who were enrolled in the clinical study that investigated A-BPO/D had an investigator’s global assessment (IGA) score of 4 (severe) on a 6-point scale from 0 (clear) to 5 (very severe).\textsuperscript{26} Patients were considered to have their symptoms controlled if they improved at least 1 score on the IGA at the end of the 12-week regimen, which indicated that the patient no longer had severe acne.

Patients who had a 1-score improvement after the 12-week regimen of A-BPO/D would be eligible for a follow-up regimen of 24 weeks of A-BPO maintenance monotherapy.

Patients whose symptoms regressed to an IGA score of 4 at the end of the maintenance regimen would have re-
pressed back to having severe acne and would have been considered to have relapsed disease. These patients would be eligible for a 20-week regimen of oral isotretinoin.

For patients who were initially treated with oral isotretinoin and did not respond to treatment, it was assumed that they would use an additional regimen of oral isotretinoin. Additional treatment was not considered for patients whose disease responded to oral isotretinoin at any point.

To calculate costs, it was assumed that 2 tubes of A-BPO would be required for the initial 12-week regimen and 4 tubes would be required for the 24-week follow-up regimen, and patients would take 1 dose of doxycycline or oral isotretinoin daily. Costs that did not account for the probability of treatment outcomes were calculated and compared using pricing described above. The expected cost of each treatment, factoring in the probability of success of each treatment, was calculated based on the following formula:

\[
\text{Expected cost} = (\text{Probability of success} \times \text{cost of success}) + (\text{probability of failure} \times \text{cost of failure})
\]

Ancillary costs for office visits, laboratory tests, and the iPLEDGE program were not considered.

**Results**

**Efficacy**

Based on the study by Gold and colleagues, patients using A-BPO/D would be expected to have an initial 72% reduction in inflammatory lesions after 12 weeks of treatment (Table 1). If those patients were using maintenance therapy of A-BPO, an additional 9% reduction would be expected, for an 81% reduction over 20 weeks (based on unpublished data). Data from clinical studies suggest that patients receiving oral isotretinoin would be expected to have an 80% to 90% reduction in inflammatory lesions after 20 weeks.

It should be noted that the A-BPO/D study design did not include nodules or cysts in the reduction of inflammatory lesions, whereas reductions in nodules or cysts were included for oral isotretinoin.28-30

No head-to-head studies have been conducted comparing A-BPO/D with oral isotretinoin that would allow direct comparisons to be made between the 2 treatments. Therefore, the comparison of efficacy in the current analysis was for descriptive purposes, because the data were not directly comparable.

**Treatment Models**

**Basic treatment model.** Table 2 shows the pricing used for the 2 models. The goal of the basic treatment model was to assess the potential savings associated with using A-BPO/D instead of oral isotretinoin for patients with severe acne vulgaris (Figure 1). The cost of the 2 drugs favors A-BPO/D over oral isotretinoin.
The cost of treatment of a 12-week regimen of A-BPO/D is between $465 and $842 per patient, with an average weekly cost of $47.86 (Table 3). The cost of a 20-week regimen of oral isotretinoin ranges from $868 to $3365.60 per patient, with an average weekly cost of $72.10. Although oral isotretinoin is more efficacious overall, A-BPO/D is less expensive in absolute drug cost and in weekly drug cost, while still effectively treating severe acne vulgaris (Figure 2).

**Long-term treatment model.** The basic treatment model only considered initial treatments and the expected efficacy associated with those treatments; however, most patients with severe acne vulgaris will require additional treatments. For the current analysis, the treatment response rates and relapse rates were compared for each regimen.

The estimated treatment response rates and relapse rates are shown in Table 4. At the end of the A-BPO/D regimen, 97% of patients would have improved at least 1 grade and would no longer have acne that is considered to be severe. Their symptoms would be considered under control, and they would be eligible for a 24-week regimen of A-BPO maintenance monotherapy. The disease of the other 3% of patients would not have improved or would have worsened and the patients would be considered to be eligible for oral isotretinoin therapy by many dermatologists.

Of the 97% of patients who received A-BPO as a maintenance therapy, 78% would be expected to continue to not have severe acne and would therefore not be eligible for oral isotretinoin. These patients’ acne would have improved or not worsened, and they would have continued to have their acne under control. In the other 22% of patients, acne would have likely worsened after a 24-week maintenance regimen of A-BPO. These patients’ acne would be considered severe, making them eligible for oral isotretinoin.

The definitions of improvement in trials with oral isotretinoin may have been different from those used for A-BPO/D. To account for the differences, it was assumed that patients who received a regimen of oral isotretinoin who would need an additional regimen would be considered to not have their acne under control for the purposes of the long-term model. For patients who were initially treated with oral isotretinoin, 22% to 39% will likely need an additional 20-week regimen of oral isotretinoin. These patients would be eligible for an additional regimen of oral isotretinoin.

A decision tree was modeled with an initial treatment option of A-BPO/D or oral isotretinoin with probable treatment outcomes and additional therapies (Figure 3). For all possible treatment outcomes, an initial regimen of A-BPO/D costs less weekly than an initial regimen of oral isotretinoin; however, these calculations did not consider the probability that a patient would receive a particular regimen. When the probability of each possible treatment outcome is factored in, the cost of treat-
ment still favors an initial treatment with A-BPO/D over oral isotretinoin (Table 5).

To achieve the goal of getting a patient’s acne under control would cost an average of $24.69 more weekly if that patient initially received oral isotretinoin.

**Discussion**

The current cost analysis shows that an initial regimen of A-BPO/D is less expensive per patient per week than an initial regimen of oral isotretinoin in treating severe acne vulgaris. Both regimens have been shown to be effective in improving severe acne.26–30 The basic treatment model compared the efficacy and costs of a single regimen of either treatment. Although no head-to-head data exist comparing the 2 treatments, patients using oral isotretinoin could expect to have the number of inflammatory lesions reduced by an additional 8% to 18% over the A-BPO/D regimen. However, such a reduction would require an additional 8 weeks of treatment and would cost an additional $24.24 per patient weekly, on average, during 12 weeks of treatment with A-BPO/D.

Patients with severe acne vulgaris frequently require additional therapy, depending on the initial treatment outcomes. A second model was developed that incorporated the probability of possible treatment outcomes on either regimen. That model assumed that patients who failed treatment with the initial A-BPO/D regimen or the A-BPO maintenance therapy would receive a 20-week regimen of oral isotretinoin. Even when the probability of receiving oral isotretinoin at some point after the initial A-BPO/D therapy was factored into the treatment costs, an initial regimen of A-BPO/D was still less expensive per patient weekly than an initial regimen of oral isotretinoin. The goal of the A-BPO/D regimen is to get acne under control so that topical medications may be used to avoid the side effects of additional oral antibiotics or oral isotretinoin.

Oral isotretinoin is recommended only for severe forms of resistant nodular/conglobate acne vulgaris.12 For less severe forms of severe acne, an oral antibiotic with a topical retinoid and a benzoyl peroxide regimen are recommended. However, oral isotretinoin is frequently prescribed for less severe acne than is indicated, in patients in whom A-BPO/D would be a more appropriate initial therapy.13

Oral isotretinoin is also associated with several severe side effects.14 It has a pregnancy category X label, indicating that it is a teratogenic drug that can cause severe birth defects. The use of oral isotretinoin also requires enrollment in the iPLEDGE program and healthcare provider visits and laboratory tests for liver function and lipid testing.15

A-BPO/D is efficacious in improving severe acne vul-
This regimen is well tolerated, with side effects that were comparable with vehicle gel plus doxycycline 100 mg, and it does not require enrollment in a REMS program. A-BPO is currently the only available fixed-dose combination topical therapy formulated with a retinoid and benzoyl peroxide.

Other available fixed-dose combination therapies combine retinoids with antibiotics, such as clindamycin. However, the antibiotic resistance of patients with P. acnes to clindamycin and other antibiotics has been reported, whereas resistance to benzoyl peroxide has not. In addition, A-BPO is suitable and is recommended for mild-to-severe acne, demonstrating its versatility in treating the disease. Therefore, A-BPO is a logical choice for a topical fixed-dose combination therapy, thanks to its efficacy, tolerability, and lack of antibiotic resistance.

Because of its efficacy and safety in treating severe acne, a regimen of A-BPO provides an alternative to oral isotretinoin, especially in patients with medical histories or conditions for which oral isotretinoin is contraindicated.

Although patients receiving oral isotretinoin may see better reductions in inflammatory lesions, that improvement comes at a higher cost, requires longer initial treatment duration, and is associated with more side effects than A-BPO. Oral isotretinoin should only be used in severe recalcitrant cases of nodular acne, because it is associated with severe side effects; however, it is frequently prescribed for less severe and even moderate cases of acne. A comparison of these 2 treatments using previously published data to evaluate efficacy and costs, modeled on a recent clinical study, demonstrates that both treatments are effective in managing severe acne and that a weekly treatment with A-BPO is less expensive than a weekly treatment of oral isotretinoin. Even when probable rates of success are considered, A-BPO is still less expensive per week than oral isotretinoin.

Conclusions

Severe acne is a serious skin disease that affects the QOL in affected individuals. A regimen of A-BPO is suitable for most cases of severe acne vulgaris and may be considered for use as a first-line therapy. Oral isotretinoin should only be used in severe recalcitrant cases of nodular acne, because it is associated with severe side effects; however, it is frequently prescribed for less severe and even moderate cases of acne. A comparison of these 2 treatments using previously published data to evaluate efficacy and costs, modeled on a recent clinical study, demonstrates that both treatments are effective in managing severe acne and that a weekly treatment with A-BPO is less expensive than a weekly treatment of oral isotretinoin. Even when probable rates of success are considered, A-BPO is still less expensive per week than oral isotretinoin.

Furthermore, ancillary medical costs, such as required laboratory tests, birth control, and the iPLEDGE program, were not considered in this analysis; those additional costs are only associated with oral isotretinoin. Therefore, the total costs of A-BPO are even likely less expensive than what is presented here. As is shown in the current analysis, A-BPO is well tolerated, efficacious, and less expensive than oral isotretinoin; for these reasons it may be considered for first-line use for severe acne with up to 3 nodules or cysts.

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Continued
Author Disclosure Statement

Dr. Penna is a partner of Formulary Resources and a consultant to Galderma Laboratories; Dr. Meckfessel is an employee of Galderma Laboratories; and Dr. Preston was an employee of Galderma Laboratories at the time of the manuscript preparation.

References


STAKEHOLDER PERSPECTIVE

Evaluating Treatments for Acne: It’s Time to “Sweat” the Smaller Things

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PHARMACY/MEDICAL DIRECTORS: Pharmacy management is changing. Our previous focus on large populations and on the small-molecule “blockbuster” drugs that are used to treat them is being deemphasized and replaced with the world of specialty pharmaceuticals that are typically used to treat small patient populations. Although specialty drugs will be the major drivers of pharmacy cost increases in 2014 and beyond, they still account for less than 25% of most pharmacy budgets.¹ The majority of pharmacy cost is associated with small-molecule drugs. In 2012, the generic prescribing rate was 84% and is currently helping to hold the cost of small-molecule drugs relatively flat, but there is still a need to actively manage the cost of
small-molecule drugs. However, it is sometimes easy to overlook savings opportunities for less-costly disease categories—“the small things.”

Dermatologic conditions account for 12.4% of all diseases that are treated by family physicians. This high prevalence is largely driven by a relatively small number of common dermatologic conditions. Acne is the most common skin disorder in the United States, affecting 40 million to 50 million Americans, with nearly 85% of all people having acne at some point in their lives. The cost of treating acne in 2004, which is the most recent year with available data, exceeded $2.2 billion, including substantial costs for prescription and over-the-counter treatments.

In their article in this issue, Penna and colleagues use existing data sources to compare the outcomes for 2 different treatment regimens for severe acne. A regimen consisting of a fixed-dose combination of adapalene and benzoyl peroxide gel, 0.1%/2.5% combined with oral doxycycline 100 mg (ABPO/D) was compared with a regimen containing isotretinoin. The clinical outcomes for these 2 regimens were similar, with some enhanced clinical benefit from isotretinoin. However, when the costs of the 2 regimens were compared, the ABPO/D treatment was substantially less expensive on a weekly basis than the isotretinoin regimen. In addition, fewer safety and monitoring issues were associated with the ABPO/D regimen compared with isotretinoin. Ultimately, the authors conclude that the ABPO/D regimen is “suitable for most cases of severe acne vulgaris and may be considered for use as a first-line therapy.”

PHARMACY & THERAPEUTICS COMMITTEE: To make informed formulary management decisions, Pharmacy & Therapeutics (P&T) committees need access to good comparative data. Although head-to-head studies that directly compare both clinical and economic outcomes are most desirable, they are generally not available for most formulary management decisions. Penna and colleagues provide the type of analysis that is becoming increasingly necessary to effectively manage clinical outcomes and cost. Although the majority of dermatologic treatments are not among the leading drivers of pharmacy cost, it is still important to find the best balance of clinical outcome and cost for the majority of patients.

Based on this study, a P&T committee can potentially develop a preferred treatment pathway that is adequate for most cases of severe acne, resulting in a win-win scenario of lower cost and a safer treatment regimen for the majority of patients. The cost-savings to a plan resulting from this pathway may not be large in absolute terms, but it is an example of cost-effective drug therapy management. Ultimately, the cumulative savings from relatively small cost categories of the pharmacy budget are essential contributors to the continued affordability of the benefit.

Prudent management of the pharmacy benefit requires attention to such detail in all disease areas. Penna and colleagues have provided us with a good example of how to manage one of those small things on the pharmacy budget with good clinical outcomes at a reasonable cost.