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Is Oral Isotretinoin More Effective than Antibiotics in the Treatment of Severe Acne in Adults?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies

Philadelphia College of Osteopathic Medicine

Philadelphia, Pennsylvania

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Abstract

Objective: The objective of this selective EBM review is to determine whether or not the use of oral isotretinoin is more effective than oral antibiotics in the treatment of severe acne.

Study Design: Review of all English language primary studies published after year 2000.

Data Sources: Three randomized control trials all found using PubMed.

Outcomes Measured: Total number and percentage change in total acne lesions from baseline at various intervals.

Results: A randomized control trial (RCT) by Gollnick et al. (2001) found that oral isotretinoin was more effective than combination therapy involving minocycline in treating severe inflammatory acne, but that isotretinoin caused more negative side effects. In a RCT by Oprica et al. (2007), it was found that oral isotretinoin was more effective than tetracycline in treating acne vulgaris with prolonged significant remission. A RCT by Tan et al. (2014) found that although doxycycline induced earlier reduction in total acne lesions, isotretinoin was still superior in reduction of acne lesions by week 20 of treatment.

Conclusions: All three RCT's included in this study indicate that oral isotretinoin is more effective than oral antibiotic therapies in the treatment of severe acne.

Keywords: isotretinoin, acne, antibiotics.

Introduction

Acne vulgaris is a common dermatosis capable of producing significant psychological and physical scarring. It is a disease of pilosebaceous follicles, involving follicular hyperkeratinization, increased sebum production, bacterial growth within the follicle, and inflammation.⁹ Therapy involving oral isotretinoin or oral antibiotics have long been mainstays of treatment of severe acne vulgaris, and this paper evaluates three randomized controlled trials comparing the overall effectiveness of each in acne treatment.

Research in treatments of acne is important to healthcare providers because acne can cause significant psychological impairment to patients, affecting their work and social lives. Acne is also the most common skin condition in the United States, affecting up to 50 million Americans annually.² The costs in the U.S. associated with the treatment of acne are greater than \$3 billion.¹ There is not an exact estimate of healthcare visits due to acne, but according to a 2010 study, there were 39 million visits to dermatology offices alone, with acne being in the top four reasons for visits.¹¹

The sequence of events leading to acne lesions is not fully understood, but lesions are brought on by plugging of the sebaceous follicle, increased sebum production, proliferation of bacteria in the follicle, and then inflammation.⁴ An estimated 35-90% of adolescents experience some form of acne, which tends to resolve by the third decade of life, but may still persist into adulthood.⁹ Acne is a clinical diagnosis, and there is no universal classification system for the severity of acne, but lesion counting and descriptions of the lesions, such as comedones, papules, pustules and nodules usually help guide treatment.⁹

Treatment of mild acne usually begins with applying topical products containing benzoyl peroxide.⁴ If that fails, second line treatment usually consists of prescription antibiotic cream,

gel, or lotion.⁴ These treatments are followed by prescription topical retinoids or azelaic acid.⁴ Acne refractory to topical medications is then treated with oral antibiotics.⁴ Finally, if all treatments fail, oral isotretinoin can be prescribed, which is usually held for last line treatment due the potential for significant side effects associated with it.⁴

Oral Isotretinoin and oral antibiotics are accepted treatment options for severe acne vulgaris, but isotretinoin is known to have more severe adverse effects than oral antibiotics, including severe birth defects and excessively dry skin.⁶ Even though both medications treat severe acne, it appears that effectiveness of isotretinoin is superior to antibiotics in reduction of total acne lesions, and therefore may be worth the risk of adverse effects for some patients with severe acne vulgaris refractory to prior treatments.

Objective

The objective of this systematic review is to determine whether or not the use of oral isotretinoin is more effective than oral antibiotics in the treatment of severe acne.

Methods

Three randomized controlled trials were included in this systematic review. The studies were selected based on populations studied, interventions used, comparisons made, and outcomes measured. The populations studied in all three RCT's consisted of patients greater than 12 years of age with moderate to severe facial acne. Gollnick et al.³ included males aged 15-31, whereas Oprica et al.⁵ included male and female patients aged 15-35, and Tan et al.⁸ included male and female patients aged 12-35.

For all studies included in this review, the intervention utilized was administration of oral isotretinoin. For Gollnick et al.³, participants received oral isotretinoin at a cumulative dose of

106-112 mg/kg for 6 months. Participants in the Oprica et al.⁵ study received oral isotretinoin at a dose of 1 mg/kg/day in two divided doses for 6 months, and participants in the Tan et al.⁸ study received oral isotretinoin at 1 mg/kg/day for 20 weeks.

Articles were researched via the PubMed database using key words such as isotretinoin, antibiotics, and severe acne, and were selected based on relevance to the clinical question and because outcomes included patient oriented evidence that matters (POEMs). All searches were set for English language and all articles searched were published in peer reviewed journals. Inclusion criteria for the purpose of this paper included randomized controlled studies that included POEMs published after the year 2000. Exclusion criteria included previous Cochrane reviews, previous student published systematic reviews, and individuals less than 12 years of age. All studies used similar statistics to evaluate the outcomes where p-value is considered statistically significant if it is less than or equal to 0.05. The demographics of the studies are included and outlined below in Table 1.

Table 1 – Demographics & Characteristics of included studies

Study	Type	#Pts	Age	Inclusion	Exclusion	W/D	Interventions
Gollnick ³ (2001)	RCT	85	15-31	Male patients with severe inflammatory acne. Severity of acne at > 4 on the Leeds scale. The face had to display at least 2 deep inflammatory lesions.	Women and patients with milder forms of acne. Patients with photosensitivity and/or allergies to treatments. Patients who have received any systemic treatment within 4 weeks of study or topical treatment within 2 weeks.	8	Isotretinoin cumulative dose of 106-112 mg/kg, PO for 6 months VS. Minocycline 100 mg daily, PO for 6 months plus topical azelaic acid cream applied BID.
Oprica ⁵ (2007)	RCT	52	15-35	Male and female patients, ages 15-35, with moderate or severe inflammatory acne vulgaris	Patients with no nodules, used oral/topical acne treatments within 8 weeks of study, used systemic retinoids within 12 months of study, receiving drugs that may interfere with tetracycline, pregnant or breastfeeding, psychiatric or systemic illness, other dermatological issues, participation in other clinical trials.	13	Isotretinoin 1 mg/kg/day in two divided doses, PO for 6 months VS. Tetracycline hydrochloride 500 mg BID plus topical adapalene once daily for 6 months
Tan ⁸ (2014)	RCT	266	12-35	Male and female patients of any race, ages 12-35, with severe facial acne vulgaris. ≥ 20 papules/pustules and ≥ 5 nodules	Pregnancy	45	Isotretinoin 1 mg/kg ⁻¹ PO QD for 20 weeks. VS. Doxycycline 200 mg PO QD plus topical agent for 20 weeks

Outcomes Measured

Each study measured the outcomes by counting the total number of acne lesions and the percentage change in either total acne lesions or specific types of acne lesions, from baseline at various intervals throughout the treatment period.

Results

In Gollnick et al.³, 85 male patients were used to compare use of oral isotretinoin and minocycline combined with topical azelaic acid cream for six months. Patients were examined at baseline and at one month intervals for the six month duration of the treatment. At each examination, the examiner counted the patient's total number of open and closed comedones, inflammatory papules and pustules, nodes, nodules and cysts. Since total acne lesions were not counted in this study, the papule and pustule counts are used for the comparison data. For the isotretinoin group, the p-value was < 0.05 , and thus proved to be statistically superior to the combination minocycline treatment throughout the six month course of the study.

Table 2. Comparison of reduction of papules/pustules at end of month 6

Intervention	% Reduction in papules/pustules	P-value
Isotretinoin	97	< 0.05
Minocycline/AA cream	88	

The Oprica et al.⁵ study employed 52 male and female patients to compare the use of oral isotretinoin and tetracycline combined with topical adapalene cream. Clinical and microbiological assessments were performed after 2, 4 and 6 months of treatment, and 2 months after cessation of treatment. Patients treated with isotretinoin showed prolonged significant

remission compared with the other group. Different types of lesions were counted at each examination, but for the purpose of this study, comparison of total lesions at month six in the male patients is utilized, although the p-value is < 0.05 in the female comparison as well. The female comparison at six months showed a 91% decrease in total lesions with use of oral isotretinoin, compared to a 63% decrease with use of the combination tetracycline therapy. The male comparison of total lesions at six months showed an 87% decrease in lesions with use of isotretinoin compared to a 43% decrease with the tetracycline, and thus demonstrated that oral isotretinoin was statistically superior to the combination tetracycline treatment at the conclusion of the six month study.

Table 3. Comparison of reduction of total acne lesions at end of month 6

Intervention	% Reduction of total lesions	P-value
Isotretinoin	87%	< 0.05
Tetracycline/topical agent	43%	

The Tan et al.⁸ study included 266 male and female patients to compare the use of oral isotretinoin with doxycycline combined with a topical agent. The participants of this study were examined for lesion counting at weeks: 2, 4, 8, 12, 16 and 20. For the purpose of this review, results are shown for the examination at week 20 when treatment is complete, and females are not excluded from this table, although they only comprise 39 of the 266 participants. By the end of the treatment course, isotretinoin again demonstrated to be statistically superior to doxycycline combined with a topical agent, with isotretinoin users showing a 93% reduction in total acne lesions compared with a 78% reduction in doxycycline users. Isotretinoin was also superior in reducing nodules (96% vs. 89%), and papules and pustules (95% vs. 80%).

Table 4. Comparison of reduction of total acne lesions at week 20

Intervention	% Reduction of total lesions	P-value
Isotretinoin	93%	< 0.01
Doxycycline/topical agent	78%	

All three studies demonstrated that isotretinoin is superior to antibiotic therapy in the reduction of acne lesions, with each study yielding a p-value less than 0.05. Using the control event rate (CER) and experimental event rate (EER), the relative benefit increase (RBI) was calculated followed by the absolute benefit increase (ABI). ABI shows an increase in treatment effect with the isotretinoin group compared to the antibiotic group. The RBI represents the effectiveness of isotretinoin and the relative probability of experiencing clinical improvement with isotretinoin treatment compared to the antibiotic treatment studied in each article. The number needed to treat (NNT) is calculated to determine the number of patients that need to receive oral isotretinoin in order to benefit one patient with symptom improvement.

Table 5. Treatment Effects

Study	P-value	CER	EER	RBI	ABI	NNT
Gollnick	< 0.05	88%	97%	101%	9%	12
Oprica	< 0.05	43%	87%	100%	44%	3
Tan	< 0.01	78%	93%	19%	15%	7

Discussion

Isotretinoin is widely known by the brand name Accutane, but this brand is no longer available in the United States. It was taken off the market in the U.S. in 2009, but alternative brands of Isotretinoin exist here in the U.S. Some of the brands available today include: Absorica, Amnesteem, Claravis, Myorisan, and Zenatane.¹⁰

Isotretinoin is a teratogenic medication, and is not to be taken if you are pregnant or are to become pregnant during the treatment course or within one month after its completion, as severe birth defects and miscarriage can occur.¹⁰ To avoid these adverse effects, it is strongly recommended for women of reproductive age to have two serum pregnancy tests obtained prior to starting treatment, and each month thereafter while using isotretinoin.⁷ It is also recommended that sexually active individuals use two forms of birth control during the duration of isotretinoin use, and it is required for men and women to register with iPledge, which is a monitoring program aimed at reducing exposure of the drug to pregnant individuals.⁷ In addition to the teratogenic effects, isotretinoin has been linked to other serious side effects and can lead to elevated liver enzymes and high triglyceride levels.⁷ For this reason, users are also required to have blood drawn every four weeks to include: complete blood cell count (CBC), cholesterol, triglyceride, and liver enzyme panel.⁷

In addition to use as a treatment for severe acne, isotretinoin has also been used to treat other conditions. For individuals with discoid lupus erythematosus, isotretinoin is considered effective at treating the hypertrophic lesions associated with the disease.⁷ Isotretinoin has also shown to be effective in the treatment of the erythematous facial flares associated with rosacea.⁷

The main limitation of this study was the small study size of two of the three articles. Oprica et al.⁵ only included 52 participants, which may not be a sufficient size to make the conclusion that isotretinoin is superior to minocycline in treatment of severe acne. Gollnick et al.³ included 85 participants, which may also be considered small for this study. This article also excluded women from the study, and did not provide statistics for reduction of the total number of acne lesions, which led to the use of reduction of papules and pustules for the purposes of this review. Tan et al.⁸ included 266 participants in the study, but despite the sufficient number of participants, only 39 were females.

Conclusion

After reviewing these three studies, evidence strongly suggests that use of oral isotretinoin is superior to oral antibiotic therapy in the treatment of severe acne in adults. Although there were flaws in the studies, primarily the small sample size and the predominance of males, the results were considered statistically significant in favor of oral isotretinoin in reducing acne lesions. Of note, oral antibiotic therapy may still be a viable alternative to isotretinoin in treatment of severe acne for some people, and these antibiotics will generally cause fewer harmful side effects than isotretinoin. Future studies are warranted that include a greater number of participants, specifically of the female gender.

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