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Oral Vitamin A for Acne Management: A Possible Substitute for Isotretinoin

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ABSTRACT

Background: Recent changes to the iPLEDGE platform left providers without the ability to prescribe isotretinoin to their patients. A potential substitute for isotretinoin could be beneficial when the drug is unavailable. Prior to the FDA approval of isotretinoin, a vitamin A derivative, vitamin A was studied for its use in acne management.

Objective: To review the potential of vitamin A to serve as a substitute for isotretinoin when the latter drug is inaccessible.

Methods: We conducted a review of published literature from 1931 to 2021, regarding the use of vitamin A in acne treatment, using PubMed and Google Scholar databases. Nine studies were selected after reviewing articles for relevancy to our topic.

Results: Eight out of the 9 studies noted improvement in patients' acne with vitamin A use. Ranges of doses used were 36,000 I/U daily to 500,000 I/U daily, with 100,000 I/U daily being the most common. Side effects were mainly mucocutaneous in nature.

Limitations: Many of the trials included in our review were published over 50 years prior and lack standardized components of clinical trials today.

Conclusion: Oral vitamin A could potentially serve as a substitute for isotretinoin in acne management for select patients. However, due to its teratogenicity, potential for toxicity, and long half-life, strict monitoring under the care of a medical provider is prudent. Since vitamin A is available without a prescription, strict monitoring cannot be assured, and especially careful patient selection and education would be essential.

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INTRODUCTION

Isotretinoin (13-cis-retinoic acid) is widely used for severe acne; however, due to its teratogenicity, it is strictly regulated.[1] iPLEDGE was implemented in 2005 to minimize the potential fetal exposure to isotretinoin.[1] The FDA announced in October 2021 that changes to the iPLEDGE system (including gender neutral options for patient risk categories and changes to the current pharmacy management system) would take effect on December 13, 2021.[2] While the new changes were welcomed by dermatologists, they were accompanied by a change in vendors and the creation of a new platform, leading to a frustrating and stressful situation for both providers and patients due to issues with accessing the iPLEDGE portal.[3] Many providers were left unable to prescribe isotretinoin to their patients, leading to a widespread disruption in patient care.[3] A potential substitute for isotretinoin could prove beneficial when the drug is unavailable or unaffordable.

Prior to the FDA approval of isotretinoin, vitamin A was widely researched for use in chemoprevention and acne treatment. The first report of vitamin A being successful in treating acne was published in 1943.[4] Following these results, the use of vitamin A for acne underwent clinical trials until isotretinoin was approved in 1982. We examined the published literature on the use of vitamin A from 1934–2021 using the databases PubMed and Google Scholar to assess its ability to serve as an alternative to isotretinoin for patients with acne. Nine studies (8 clinical trials and one case study) were included after evaluation for relevancy to the topic of interest.

Of the 9 trials reviewed, 8 had improvement in patients' acne using vitamin A (Table 1). Treatment doses ranged from 36,000 IU daily to 500,000 IU daily.[4–12] Forty-four percent of trials used 100,000 IU daily with success. Treatment lengths ranged from one month to seven months. Mean duration until clinical improvement ranged from 7 weeks to 4 months after initiation of therapy. Relapse was noted in 33% of the trials included, however, this is comparable to the relapse rates (13–42%) noted for isotretinoin. In the clinical trials reviewed for both vitamin A and isotretinoin, the most frequent side effects were mucocutaneous, such as cheilitis and xerosis. At doses of 500,000 IU daily, mucocutaneous side effects were more severe, however, no serious side effects were noted. Benign elevations

TABLE 1.
Improvement in Patients' Acne Using Vitamin A

Author	Date of Trial	Number of Patients	Type of Trial	Gender	Average Age	Baseline Severity Levels	Treatment	Length of Treatment	Side Effects	Relapse Rates	Outcome Measures	Outcomes
Straumfjord et al.[4]	1943	100	Prospective	n/a	n/a	n/a	100,000 IU oral vitamin A daily in oil	6 months	Increased skin aggravation at be-ginning of treatment	n/a	n/a	79% of patients were free of acne at end of trial Improvement was not noticed until 3rd month of treatment, often 6 months was needed for complete clearance of disease
Cook et al.[5]	1947	52	Prospective	4/12 males (33.3%), 8/12 females (66.7%)	Univer-sity students	n/a	100,000 IU oral vitamin A daily	4-5 months	n/a	n/a	n/a	73% of patients had improvement in their acne
Savitt et al.[6]	1948	65	Prospective	39% (17/43) males, 61% (26/43) females	20.6 years	Mild to moderate	100,000 IU oral vitamin A daily or placebo	1-7 months	n/a	n/a	n/a	57% of patients in experimental group showed improvement in their acne compared to 4 (50%) of those in placebo group.
Davidson et al.[7]	1949	30	Prospective	10/20 (50%) males, 10/20 (50%) females	18.2 years	Mild, moderate, severe	36,000-40,000 IU aqueous vitamin A dispersion daily	2-5 months	2 patients had to stop the medication due to abdominal pain and severe diarrhea One patient with epilepsy noted her epilepsy to be worsened while on the treatment and to improve following cessation of the treatment	8 patients experienced recurrence of acne within 4 months following dis-continuation of therapy	Criteria of improvement was based on the degree of lessened outbreaks of new lesions in addition to involution of old ones	7/30 (23.3%) were almost clear at the end of treatment 9/30 (30%) were moderately improved after treatment, 2/30 (6.7%) were completely clear at the end of treatment 2/30 patients (6.7%) had no improvement after completion of treatment, although one of these patients was taking the medication irregularly
Mitchell et al.[8]	1951	30	Prospective	15/30 (50%) males, 15/30 (50%) females	Children	Ranged from com-edones, papules, to pustules and cysts	100,000 IU intramuscular vitamin A or 100,000 IU oral vitamin A in oil three times/week or placebo	2-5 months	Side effects all were related to site of injection which ranged from pain, discomfort, to swelling of the injection site No side effects were noted in the group receiving oil vitamin A	n/a	Photographs from 2 days before treatment and one week after were used to determine improvement	2/9 (22.2%) patients in the vitamin A oil solution group showed improvement after treatment 1/10 (10%) of patients who received vitamin A intragluteal showed improvement after treatment 2/11 (18.2%) of the patients in the control group showed improvement after treatment
Kalkoff et al.[9]	1956	229	Prospective	n/a	n/a	Moderate to severe	100,000-400,000 IU daily + mainte-nance dose of 25,000-65,000 IU daily	6 months	Were considered "few and slight" Elevated LFTs in those receiving 400,000 IU daily	Relapse present in some after finishing treatment	n/a	93.33 % of patients in the experimental group showed improvement in their acne Mean duration until clinical improvement was around 7 weeks

TABLE 1. CONTINUED

Improvement in Patients' Acne Using Vitamin A

Author	Date of Trial	Number of Patients	Type of Trial	Gender	Average Age	Baseline Severity Levels	Treatment	Length of Treatment	Side Effects	Relapse Rates	Outcome Measures	Outcomes
Stokoe et al.[10]	1963	80	Prospective	34/80 male (42.5 %) 46/80 female (57.5%)	n/a	n/a	150,000 IU oral vitamin A daily or placebo tablets of starch 110mg, talc 2mg, lactose 10mg	12 weeks	n/a	n/a	Photographs were taken at the beginning and end of the trial to assess improvement	49.2% of patients in experimental group showed improvement in their skin compared to 50.8% of patients in placebo group Of 13 people who had worsened results, only 2 were in the experimental group
Kligman et al.[11] (split trial)	1981	136	Prospective	80/136 (58.8%) males, 56/136 (31.1%) females	Late adolescence to young adulthood	All patients had serious, inflammatory acne with facial lesions consisting of papules, pustules, and variable nodules	300,000 IU oral vitamin A daily	4-5 months	75% had cheilitis 5% had minor nosebleeds 6.6% had headache Average TGA level was 197 in group with gradual increase to 500,000 IU oral vitamin A for 12 weeks	Relapse rates within 4-6 weeks after completion of therapy were common	Measurements of sebum production Therapeutic response was observed globally with >75% improvement indicating excellent response, 50-75% indicating good response, 25-50% improvement indicating fair response, and 0-25% improvement indicating poor response	50.7% had excellent improvement response indicating greater than 75% improvement and 41.2% of patients had a "good" response indicating 50-75% improvement in their acne. There was 30% decrease in sebum production within 10 weeks of treatment 3-4 months were required to clear deeper, cystic lesions
		30	Prospective	All males			300,000 IU oral vitamin A daily or 300,000 IU daily for first week, 400,000 IU for second week, and 500,000 IU daily for last 10 weeks	12 weeks	Average TGA level was 164 in group with 300,000 IU oral vitamin A for 12 weeks Some minor increase in serum LFTs in some patients			Of the patients receiving 300,000 IU oral vitamin A daily, 20% had an excellent response, 70% had a good response Of the patients who received sequential doses of 300,000, 400,000, and 500,000 IU oral vitamin A daily, 50% had an excellent response and 50% had a good response after 12 weeks of treatment
Drake et al.[12]	2019	1	n/a (case report)	1 male	14	Cystic acne with involvement of the entire face	100,000 IU oral vitamin A daily for one week, followed by 200,000 IU daily for 3 months	4 months	Cheilitis and xerosis of skin on face that resolved within 2 months of treatment	No relapse for 6 months after treatment completion	n/a	Complete remission of acne after 4 months of treatment

in triglycerides and liver enzymes occurred in some patients, but they returned to baseline within 2–3 weeks after stopping treatment, similar to isotretinoin.

While oral vitamin A appears efficacious for mild to severe acne, studies done years ago would not meet current standards for drug approval, and our ability to provide a truly critical appraisal of the differences and similarities between oral vitamin A and isotretinoin is limited by the contrast in quality of isotretinoin and vitamin A trials. Side effects of oral vitamin A are similar to those of isotretinoin, including, importantly, teratogenicity. Acute vitamin A toxicity has been reported at initial doses of 25,000 IU/kg and chronic toxicity has been reported at doses of 4,000 IU/kg daily for a duration of 6–15 months.[13] Signs of mild toxicity, such as mucocutaneous symptoms, are expected at the doses required for acne management and are similar to those of isotretinoin. Laboratory monitoring includes liver function tests, lipids, and pregnancy tests, in females of childbearing potential, as would be done with isotretinoin. The half-life of vitamin A is much longer than that of isotretinoin (12 days versus 24–29 hours, respectively), and female patients of childbearing age should be advised to wait at LEAST 3 months following treatment cessation before conceiving.[14] Vitamin A is affordable and readily accessible over the counter in unit doses of 5,000 to 25,000 IU per capsule for about one tenth of the cost of isotretinoin.[15] At doses of 50,000–300,000 IU daily, vitamin A may provide a substitute for acne management *when isotretinoin is unavailable*. Recommending an over-the-counter vitamin to which patients could have unlimited access without supervision by a medical provider should be done with very careful attention to patient selection and education.

DISCLOSURES

The authors declare the following potential conflicts. Dr. Steven Feldman has received research, speaking, and/or consulting support from a variety of companies including Galderma, GSK/Stiefel, Almirall, Leo Pharma, Baxter, Boeringer Ingelheim, Mylan, Celgene, Pfizer, Valeant, Taro, Abbvie, Cosmederm, Anacor, Astellas, Janssen, Lilly, Merck, Merz, Novartis, Regeneron, Sanofi, Novan, Parion, Qurient, National Biological Corporation, Caremark, Advance Medical, Sun Pharma, Suncare Research, Informa, UpToDate and National Psoriasis Foundation. He is founder and majority owner of www.DrScore.com and founder and part owner of Causa Research, a company dedicated to enhancing patients' adherence to treatment. Madison K. Cook and Patrick O. Perche have no conflicts of interest to report.

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