Safe use of therapeutic dose oral isotretinoin in patients with a history of pseudotumor cerebri.

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Abbreviations:
CSF: cerebrospinal fluid
DHEAS: dehydroepiandrosterone sulfate
PCOS: polycystic ovarian syndrome
PTC: pseudotumor cerebri

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Abstract

Importance: Commonly used medications in the treatment of acne, including minocycline, doxycycline, and isotretinoin, are known to be associated with the development of pseudotumor cerebri (PTC). Use of these medications (in particular, isotretinoin) may often be avoided in patients with a history of PTC, even if the clinical severity of disease would otherwise indicate isotretinoin treatment. There is a paucity of data in the medical literature on the safety of isotretinoin in patients with a history of PTC (either idiopathic or drug-associated).

Observations: We report the safe and efficacious use of isotretinoin in total cumulative doses of 120 to 140 mg/kg in 3 patients with histories of drug-associated PTC, 2 of whom had developed PTC in association with minocycline and one of whom developed PTC in association with a prior course of oral isotretinoin.

Conclusions and Relevance: We suggest that in patients whose acne truly warrants isotretinoin treatment, a history of PTC should not absolutely preclude its use, when careful surveillance for recurrence of PTC can be appropriately conducted. Our conclusion is based on our experience in 3 patients, and additional clinical data on the safety of isotretinoin in patients with a history of PTC is needed.

Introduction.

Pseudotumor cerebri (PTC) is a syndrome of increased intracranial hypertension defined clinically by headache, papilledema, and vision loss, which may be severe and permanent. PTC has been reported in association with drugs commonly used in the treatment of acne vulgaris, specifically, the tetracyclines (most commonly minocycline) and oral isotretinoin. Thus, these medications are often avoided in the treatment of acne in patients with a history of PTC. We report the safe use of therapeutic doses of oral isotretinoin in three patients with a history of drug-associated PTC.

Case 1.

An 18-year-old female with a 2-year history of severe, nodulocystic acne of her face, chest and back with significant scarring was referred to Penn State Hershey Dermatology for management of acne. Of note, when she received minocycline for acne treatment approximately 2 years previously, she had developed a persistent headache; a diagnostic and therapeutic lumbar puncture confirmed pseudotumor cerebri (PTC). Minocycline was suspected as the cause and was promptly discontinued. Symptoms of PTC did not recur.

The patient had also previously received adapalene 0.1% gel, clindamycin-benzoyl peroxide gel, benzoyl peroxide wash, and erythromycin for her acne. In addition, a cyst excision was performed 3 months prior to presentation, resulting in a large linear scar across her right cheek (Figure 1). At her first visit to our clinic in March 2013, plaques of confluent cysts, sinus tracts, and the aforementioned scar were noted (Figure 1). Her current regimen consisted of norgestrel and ethinyl estradiol (Lo Ovral®), benzoyl peroxide wash daily, and clindamycin-benzoyl peroxide gel daily. Intralesional triamcinolone 10 mg/mL in a total amount of 0.5 mL was administered to multiple cysts on each cheek, and the patient was

started on spironolactone 50 mg twice daily. Dehydroepiandrosterone sulfate (DHEAS), free and total testosterone levels were tested and were within normal limits.

For the next 2 months, the patient required increasing doses of spironolactone, to 200 mg daily, with continued norgestrel and ethinyl estradiol and clindamycin-benzoyl peroxide gel. At each visit she also received intralesional triamcinolone injections to multiple cysts. Little improvement was observed, with cysts recurring by each 4-week follow-up visit.

Given the refractoriness of the patient's acne, isotretinoin therapy was initiated at a dose of 10 mg daily for 7 days followed by 20 mg daily thereafter; oral prednisone 40 mg daily was added to minimize flaring. Spironolactone 200 mg daily and norgestrel and ethinyl estradiol were continued.

One month later, the patient was doing well, without any side effects or symptoms concerning for PTC. Isotretinoin was increased to 30 mg daily and her dose of prednisone was tapered off. After 3 months of isotretinoin therapy without any report of headache or visual changes, isotretinoin was increased to 40 mg daily, and continued at that dose for 5 more months to a total cumulative dose of 120 mg/kg. Dryness and erythema were her only notable side effects during the entire course of isotretinoin. After the total of 9 months of therapy, her acne had markedly improved and she was extremely satisfied with the results (Figure 2).

Case 2.

A 29-year-old female with polycystic ovarian syndrome (PCOS) and a long history of acne vulgaris presented to University of Alabama-Birmingham Dermatology for a second opinion. Over the past 15

years, she had been treated with adapalene 0.3% gel, tazarotene gel, tretinoin cream 0.025%, benzoyl peroxide-erythromycin gel, sodium sulfacetamide lotion, amoxicillin, trimethoprim-sulfamethaxole, ampicillin, dapsone, spironolactone, oral contraceptives, and benzoyl peroxide washes, in various combinations, none of which adequately controlled her disease. Multiple providers had avoided isotretinoin treatment for almost the entire length of her disease history because at age 16, she had been diagnosed with minocycline-induced PTC. She had developed headaches and papilledema after starting minocycline 100 mg daily for acne. A lumbar puncture had confirmed PTC and minocycline was discontinued with resolution of PTC symptoms.

At presentation in April 2013, severe inflammatory and nodular acne with scarring was noted (Figure 3). Her therapeutic regimen at the time consisted of tazarotene gel 0.1% gel, dapsone gel, and drosperinone-ethinyl estradiol (Yaz®). Due to the severity of her skin disease and inadequate efficacy of other therapies, isotretinoin treatment was discussed with the patient.

In June 2013, the patient was started on isotretinoin 30 mg daily (with continuation of drosperinone-ethinyl estradiol). After one month of therapy, she reported dryness as the only side effect, and her dose was increased to 60 mg daily. Two months later, she still reported only dryness, denied headache and visual changes, and her isotretinoin dose was increased to 80 mg daily. She did develop hypertriglyceridemia (274 mg/dL) (repeated fasting level, (288mg/dL)), for which she was started on fenofibrate 48 mg daily.

After 5 months of isotretinoin treatment, no active acne was visible. Her regimen of isotretinoin 80 mg daily, fenofibrate and drosperinone-ethinyl estradiol was continued for one more month to reach a total cumulative dose of 11,100 mg (approximately 140 mg/kg) of isotretinoin.

At follow-up one year later, the patient was extremely happy with treatment, with only mild scarring present (Figure 4).

Case 3.

A 17-year-old female with severe, scarring nodular acne presented to Jefferson Medical College Dermatology for further acne management. Her history included a previous course of oral isotretinoin 3 years earlier (unknown course and dose) during which she developed severe headaches and vision changes. At that time, a neurologist and ophthalmologist had confirmed the diagnosis of PTC, and oral isotretinoin was discontinued.

Her acne recurred and was resistant to trimethoprim-sulfamethoxazole, spironolactone, and multiple formulations of topical retinoids and other oral antibiotics. In concert with ophthalmology and neurology consults, oral isotretinoin was initiated at a dose of 10 mg daily, gradually increased to 30 mg daily, and continued to a total cumulative dose of 120 mg/kg. During isotretinoin treatment, monthly eye exams were performed to monitor for any development of papilledema. Her acne improved dramatically, with no recurrence over several years of follow-up.

Discussion.

Pseudotumor cerebri (PTC) is characterized by symptoms related to increased intracranial pressure and brain edema: headache, visual changes (blurry vision, diplopia), nausea and vomiting, and stiff neck.[1] PTC is commonly idiopathic, primarily affecting women of childbearing age who are overweight, or, less

frequently, can occur in association with other disease etiologies (usually endocrinological abnormalities such as PCOS), vitamin deficiencies and excesses, or hereditary conditions.[2] While no significant differences in PTC epidemiology, symptomatology, and drug associations seem to exist between the pediatric population and adults, a 2006 study suggested that pubertal (defined as ages 9 to 16 years, non gender-specific) patients had a less favorable visual outcome than pre-pubertal and adult patients.[3]

Despite many anecdotal reports of drug-associated PTC, there are only three drugs (or classes of drugs) considered by experts to have a true association with PTC:[1,4] 1), tetracyclines, including doxycycline and minocycline; 2), oral retinoids; and 3), recombinant (synthetic) growth hormone. In addition, corticosteroid withdrawal has been associated with PTC.[1,4] Cross reactivity between these drug classes in patients with a history of drug-induced PTC has not been reported.

Symptoms of drug-associated PTC usually regress upon discontinuation of the drug.[1,5] However, a severe case of papilledema and visual field loss, both persisting more than 3 months after minocycline discontinuation, has been reported.[6] This patient required placement of a ventriculoperitoneal shunt for elevated intracranial pressure despite oral acetazolamide therapy and had persistent visual field loss at 6 months of follow-up.[6]

The pathophysiological mechanisms of drug-associated PTC are not fully understood. It has been postulated that the tetracyclines may mediate cyclic adenosine monophosphate production, leading to a reduction of cerebrospinal fluid (CSF) outflow at the arachnoid villi and consequent intracranial edema and increased intracranial pressure.[6,7] Oral retinoids may also reduce CSF resorption: Levels of serum retinol binding protein are elevated in patients with idiopathic PTC compared to normal controls,[8] and excess retinol and retinol binding protein may be toxic to the function of the arachnoid villi.[9]

We suspect that isotretinoin may be frequently avoided in patients with a history of PTC in whom isotretinoin would otherwise be indicated for treatment of severe acne. Indeed, when considering isotretinoin use in the 3 patients presented in this report, we found a paucity of data in the medical literature relating to this topic. There is one report of isotretinoin use in a patient with a history of minocycline-induced PTC, though the authors did not reach therapeutic dosing of the drug (the total cumulative dose was 65 mg/kg).[10]

We report the safe use of isotretinoin in total cumulative doses of 120 to 140 mg/kg in 3 patients with histories of drug-associated PTC, 2 of whom developed PTC in association with minocycline and one of whom developed PTC in association with a prior course of oral isotretinoin. We suggest that in patients whose acne truly warrants isotretinoin treatment, a history of PTC should not absolutely preclude its use, when careful surveillance for recurrence of PTC can be appropriately conducted. Prior to initiation of oral isotretinoin, baseline evaluation by ophthalmology and/or neurology services should be considered, particularly in patients with a history of severe or persistent clinical symptomatology related to PTC.

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Author Contributions:

Dr(s) Tintle, Thiboutot, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Thiboutot. Acquisition, analysis, and interpretation of data: Tintle, Thiboutot. Drafting of the manuscript: Tintle, Thiboutot. Critical revision of the manuscript for important intellectual content: Tintle, Thiboutot, Harper, Webster. Statistical analysis: Not applicable. Obtained funding: None. Administrative, technical, or material support: Tintle, Thiboutot. Study supervision: Thiboutot.

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Figure Legends.

Figure 1. Patient 1, prior to isotretinoin treatment. Severe nodulocystic acne with large linear scar from prior cyst excision.
Figure 2. Patient 1, after 8 months of isotretinoin treatment (120 mg/kg total cumulative dose). Despite a thin layer of makeup, marked improvement of acne can be appreciated.
Figure 3A, B. Patient 2, before isotretinoin treatment.
Figure 4A, B. Patient 2, following 6-month course of isotretinoin therapy (140 mg/kg total cumulative dose).