Safety Considerations and Monitoring in Patients Treated with Systemic Medications for Acne

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KEYWORDS

• Acne • Systemic treatments • Safety • Monitoring • Oral antibiotics • Spironolactone • Isotretinoin

KEY POINTS

- Minocycline-induced autoimmunity and hypersensitivity reactions have been increasingly reported in the last few decades.
- Doxycycline is rarely associated with serious adverse effects over more recent years.
- There is literature to support that routine monitoring of serum potassium levels in healthy young women taking spironolactone for acne is not necessary.
- Ocular adverse effects of isotretinoin may need to be communicated to the patients more actively for better safety monitoring.
- Low-dose intermittent isotretinoin regimen has been reported effective.

INTRODUCTION

Acne vulgaris is one of the most commonly encountered conditions in dermatology practice. It is a disorder of the pilosebaceous unit and affects about 33% of individuals between the ages 15 and 44 years, primarily adolescents.[1] Effective treatment of acne vulgaris is important in that it can prevent psychosocial distress and physical scarring. Various therapeutic options are available according to the severity of the disease. Although a broad proportion of patients with acne can be successfully treated using topical agents such as benzoyl peroxide, topical antibiotics, and topical retinoids, patients with moderate to severe inflammatory acne require systemic therapy. This article is a concise review of side effects and monitoring guide for the most commonly prescribed systemic agents for acne vulgaris.

TETRACYCLINES

Tetracyclines are the most commonly prescribed antibiotics for the treatment of acne. Compared with the original tetracycline, the second-generation synthetic molecules, doxycycline and minocycline, offer easier dosing schedules and are more readily absorbed when taken with food.[2] They are bacteriostatic and work on inhibition of bacterial protein synthesis. Serious side effects associated with tetracyclines are rare in its use for acne, but as an antibiotic class, more common side effects of doxycycline and minocycline include gastrointestinal symptoms with nausea, vomiting, and diarrhea; pediatric teeth discoloration; central nervous system effects such as dizziness and light headedness; and candidiasis.[2,3] Photosensitivity and photo-onycholysis are also seen,[4] however, sun protection with daily

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sunscreen wear may help prevent treatment-related sunburns. Doxycycline and minocycline offer similar efficacy for management of acne,[5–7] but they differ in their side-effect profiles. Recent literature reviews have compared the safety profiles of doxycycline and minocycline.[2,3]

In their systematic review of safety of doxycycline and minocycline, Smith and and Leyden noted that there were more than 3 times as many new prescriptions for doxycycline than for minocycline in the United States from 1998 to 2003. And the adverse event rates for the same period were 5 times greater for minocycline than doxycycline based on the US Food and Drug Administration's MedWatch Adverse Event reporting program data. Analysis by Smith and Leyden[2] also found that gastrointestinal effects were the most common adverse effects related to doxycycline use, whereas central nervous system and gastrointestinal effects were most common with minocycline. In this 2005 article, Smith and Leyden[2] made an observation regarding the kinds of adverse effects that differed from clinical trials and published case reports. For doxycycline, the types of adverse effects in published case reports were similar to those reported in clinical trials. However, those for minocycline were significantly different, with events that range from minocycline-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome with persistent myocarditis to minocycline-induced autoimmunity (MIA).[8,9] The authors noted that case reports represent something of clinical interest to the medical community and generally reflect less frequent but more serious adverse effects. However, taken collectively, the patterns of reported adverse events can suggest a causal relationship between the drug and event, justifying further investigation.[2]

According to Kircik[3] in his 2010 article, data indicate that MIA may lead to chronic symptoms, persisting from 13 to 48 months.[10] Pathogenesis of MIA has not yet been established, although it is suspected to be similar to other drug-induced autoimmunity.[3] Female patients are more commonly affected than male patients. The average age of onset of MIA was between 13 and 18 years with mean duration of minocycline therapy of 13 months for those with transient MIA, 14.6 months for those with intermediate, and 11.8 for those with chronic MIA. The median estimated cumulative minocycline dose in each of the 3 groups was 72 g, and most patients had a positive family history of autoimmune disorder.[10]

Minocycline is also associated with potentially fatal hypersensitivity syndrome or DRESS.[8,11] Predictive factors are not well defined, but recent evidence suggests that minocycline-induced DRESS occurs mainly in patients with Fitzpatrick skin phototypes V and VI.[12] Although the incidence of minocycline-induced DRESS is rare, its widespread use necessitates awareness among physicians who are initiating systemic antiacne therapy in patients, especially those with skin types V and VI.

Doxycycline, however is viewed as the safest within the tetracycline class, with fewer reported cases of side effects.[13] It is available in 2 different formulations: doxycycline hyclate and doxycycline monohydrate. Doxycycline hyclate is more acidic than doxycycline monohydrate and may be associated with a higher risk of esophageal ulceration if the drug is taken without sufficient water.[3] The development of enteric-coated doxycycline hyclate has been linked to a decrease in gastrointestinal side effects.[14] Also, taking it with adequate amount of water is found to significantly decrease the risk of esophageal ulceration.[4] Studies support the benefit of enteric-coated doxycycline to decrease nausea, vomiting, and abdominal pain compared with both conventional doxycycline hyclate capsule and doxycycline monohydrate.[15,16] Despite its favorable safety record, several serious doxycycline-induced adverse reactions have emerged over the last few years.[17] There are several case reports of doxycycline-induced pseudotumor cerebri in acne patients and DRESS syndrome after doxycycline treatment.[18–21] One case of doxycycline-induced cutaneous inflammation with systemic symptoms was also reported in a 15-year-old patient taking doxycycline for 2 years.[17] A brief summary of adverse reactions to minocycline and doxycycline is outlined in **Table 1**.

SPIRONOLACTONE

Although not approved by the US Food and Drug Administration for the treatment of acne, spironolactone, a medicine that blocks androgen receptors, is found to be effective in treating acne vulgaris, at daily dosage of 100 to 200 mg, in most women and adolescent girls, especially those with worsening acne associated with menstrual cycle.[31–34] The incidence of side effects at this dose may be high, ranging from 75% to 91%, but the severity is generally mild with good tolerance by most women.[35] Reported side effects included menstrual irregularities and central nervous system side effects such as headache and dizziness.[36] More recent data support the efficacy of lower doses of spironolactone at 50 to 100 mg daily, which were much better tolerated.[31,35,37,38] The main side effect reported at this dose was mild, clinically insignificant elevation of serum