

## IN-DEPTH REVIEWS

## Capsule Commentaries: Drug Reaction Considerations with Oral Minocycline

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## ABSTRACT

Minocycline is a commonly prescribed oral antibiotic in dermatology with a favorable efficacy and safety profile, and with clinical applications for a variety of cutaneous infections and other skin disorders. Most patients do not experience any adverse events, although, rare but potentially serious side effects can emerge. In this article, drug hypersensitivity syndrome, hepatotoxicity, and pseudotumor cerebri associated with oral minocycline use are reviewed.

## INTRODUCTION

Oral minocycline is one of the most commonly prescribed antibiotics in dermatology, most frequently used for the treatment of acne vulgaris (AV), but also utilized to treat cutaneous infections caused by a variety of organisms, such as *Staphylococcus aureus* (including methicillin-resistant strains [MRSA]) and atypical *Mycobacterium spp.*<sup>1-4</sup> Minocycline is also a viable oral therapy option for the short-term treatment of papulopustular rosacea (PPR) in cases where oral doxycycline cannot be used, however, subantibiotic dosing with oral minocycline is not available; oral minocycline may also be used for the treatment of many cutaneous infections where doxycycline is used, such as staphylococcal infections, some mycobacterial infections, Lyme disease, and

selected rickettsial diseases.<sup>3-6</sup> In a case report of atypical mycobacterial infection (eg *M marinum*), oral minocycline was shown to be effective after failure with a 4-week course of oral doxycycline.<sup>7</sup>

Along with its successful use in many patients with non-infectious inflammatory dermatoses such as AV, and for several types of cutaneous infections, oral minocycline, (like other tetracyclines) is associated with an overall favorable safety profile since its release into the marketplace in 1971.<sup>2,8,9</sup> Nevertheless, oral minocycline may induce an array of potential side effects that are much more uncommon with or do not occur with other tetracycline agents.<sup>2,9-16</sup> This article highlights some uncommon but potentially serious adverse events (AEs) that

may develop in association with the use of oral minocycline. Some AEs induced by oral minocycline may occur within days of initiation of therapy (eg vertigo/dizziness, urticaria), others within 2 weeks to a few months (eg drug hypersensitivity syndrome, serum sickness-like reaction (SSLR]), and still others occur usually after prolonged therapy over several months to years (eg hyperpigmentation, autoimmune reactions).<sup>2,10-14,16</sup>

### DRUG HYPERSENSITIVITY SYNDROME (DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS [DRESS])

Drug hypersensitivity syndrome (DHS), also referred to as DRESS, is an uncommon AE that has been associated with certain drugs, such as aromatic anticonvulsants (eg phenytoin), allopurinol, and minocycline, developing usually within 2 to 8 weeks after initiation of therapy.<sup>2,10,11,14,17-19</sup> Affected patients often present with facial and peripheral edema, an exanthem, fatigue, fever, eosinophilia (in most cases), and a variety of systemic associations related to interstitial inflammation; hepatotoxicity is seen in most cases, with other organ systems also affected in some cases (eg pneumonitis, nephritis, vasculitis, cerebritis, delayed-onset thyroiditis).<sup>11,14,17</sup>

**Commentary:** Early recognition, discontinuation of the causative drug, prompt initiation of systemic corticosteroid therapy, and appropriate supportive care are strongly recommended.<sup>17,19</sup> In cases induced by minocycline, rechallenge with minocycline or other tetracyclines is not recommended due to the severity and morbidity associated with DHS (DRESS).<sup>14</sup>

### HEPATOTOXICITY

Hepatitis associated with tetracycline agents is rare, including with doxycycline and minocycline.<sup>2,10-12</sup> In the case of minocycline, onset may be early, usually as a component of DHS, or after a prolonged duration of several months to years, most often as autoimmune hepatitis; the latter also presenting in some cases as part of minocycline-induced lupus-like syndrome (LLS).<sup>2,10,13-18,20,21</sup> If hepatotoxicity associated with minocycline use is suspected or detected, it is important that the drug be discontinued immediately and both diagnostic efforts and management be initiated.<sup>2,11,14,16,17,20</sup> In cases of hepatotoxicity with autoimmunity/LLS associated with minocycline use, antinuclear antibody (ANA) positivity is present, and other autoantibodies may also be detected in some cases.<sup>2,16,17,20</sup> Many cases resolve upon drug discontinuation, however, some require immunosuppressive therapy.<sup>16</sup>

**Commentary:** Awareness regarding potential hepatotoxicity, both of early onset or late onset, is important when prescribing oral minocycline. These reactions are rare, but must be kept in mind to optimize detection. Although routine laboratory monitoring is not recommended with oral minocycline use, baseline ANA and liver enzyme (eg transaminase) testing have been suggested when prolonged therapy with oral minocycline is anticipated (eg >1 year).<sup>14</sup>

## BENIGN INTRACRANIAL HYPERTENSION (PSEUDOTUMOR CEREBRI)

Benign intracranial hypertension, commonly referred to as pseudotumor cerebri (PTC), is a relatively uncommon, but highly clinically significant potential adverse reaction associated with some medications. Although disease states and not medications may be the cause of PTC in some cases, certain systemic drugs such as tetracyclines (eg tetracycline, minocycline, doxycycline), vitamin A, isotretinoin, and withdrawal from corticosteroids have been associated.<sup>2,22,23</sup> Cases of PTC induced by minocycline have been reported, with onset within weeks of starting the drug, or after several months of use.<sup>23-26</sup> PTC often presents with severe/refractory cephalgia (often worsened with postural changes such as lying down, bending over), diplopia, photophobia, visual loss, transient visual changes, pulsatile tinnitus, nausea, and/or vomiting.<sup>22,23</sup> It is important to discontinue the suspected offending drug when PTC is suspected, and to arrange diagnostic examination by an ophthalmologist as immediately as possible; many cases resolve with prompt discontinuation of the causative agent (eg oral minocycline), although, prolonged visual changes/loss occurs in some cases.<sup>22-26</sup> Among the tetracyclines, the relative incidence is 4,400/100,000/year with minocycline and 110/100,000/year with doxycycline.<sup>23</sup>

**Commentary:** It is important to maintain a high index of suspicion for PTC in a patient using an oral tetracycline if there is emergence of refractory headaches, symptoms that affect their vision, and pulsatile tinnitus. The risk of PTC appears to be higher with oral minocycline. If symptoms suggestive of PTC develop in a patient

taking a tetracycline agent such as minocycline, immediately have the patient stop the drug and promptly arrange for consultation with an ophthalmologist.

## SUMMARY

Oral minocycline is a very commonly prescribed antibiotic in dermatology due to a favorable efficacy and safety profile, and a broad range of clinical applications for a variety of infections and other cutaneous disorders. Most patients do not experience significant side effects, although, rare but potentially serious adverse events can occur. This article reviews some of these rare side effects that may be induced by minocycline to assist clinicians in prompt recognition and appropriate management.

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