

Oral Trimethoprim/Sulfamethoxazole in the Treatment of Acne Vulgaris

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Oral trimethoprim/sulfamethoxazole (TMP-SMX) is approved by the US Food and Drug Administration for the treatment of urinary tract infections, shigellosis, acute otitis media in pediatric patients, and Pneumocystis carinii pneumonia. TMP-SMX has been used off label in dermatology to treat various skin conditions, including acne vulgaris and other skin and soft tissue infections, especially those infections caused by methicillin-resistant Staphylococcus aureus.

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Acne vulgaris is a common disorder of the pilosebaceous unit. Tetracycline has been used in the treatment of acne vulgaris since the mid to late 1950s, with doxycycline and minocycline becoming available in 1967 and 1972, respectively.¹ Tetracycline antibiotics have been shown to be effective in most patients, though some patients may show less than adequate response, which may be because of factors such as the presence of less sensitive *Propionibacterium acnes* strains, poor compliance, and adverse effects. Oral trimethoprim/sulfamethoxazole (TMP-SMX) was found to be effective in patients who were refractory to tetracycline use for acne

vulgaris.² TMP-SMX may be advantageous because of the synergistic effects of its 2 antibacterial agents, the bactericidal activity, the drug's potential ability to decrease the emergence of resistance because of its individual components, and the lack of widespread or chronic use in the United States in the patient population most commonly treated for acne vulgaris.²⁻¹⁰

What efficacy data is available on the use of TMP-SMX for the treatment of acne vulgaris?

The use of TMP-SMX (trimethoprim 80 mg/sulfamethoxazole 400 mg) as monotherapy in the treatment of acne vulgaris was first reported in 1971 by Cotterill et al² who compared the drug's effectiveness with that of oxytetracycline. The study included 42 subjects aged 12 to 32 years who were randomly selected to receive 250 mg of oxytetracycline or TMP-SMX for 3 months. TMP-SMX was shown to be equally effective as oxytetracycline in the treatment of acne vulgaris.²

Hersle⁴ conducted a double-blind, randomized, crossover trial that involved 43 subjects started on one tablet daily of TMP-SMX or placebo in a 5-week period. The results of the trial revealed a greater reduction in acne lesions in subjects treated with TMP-SMX than in subjects treated with placebo. Hersle⁴ also noted that 2 subjects previously treated unsuccessfully with tetracyclines exhibited remarkable improvement when treated with TMP-SMX. Macdonald et al⁷ also showed TMP-SMX to be effective in acne vulgaris, especially in reducing the number of pustules and open comedones.

Jen⁸ conducted a double-blind randomized study involving 30 subjects who received 4 weeks of either TMP-SMX twice daily or oxytetracycline 250 mg twice daily, followed by 8 weeks of the opposite agent administered once daily. Similar to results reported earlier by Cotterill et al,² Jen⁸ found that

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TMP-SMX was as effective as oxytetracycline in the treatment of acne vulgaris.

Oral trimethoprim has been recommended as a third-line oral antibiotic in the management of acne vulgaris based on an open-label randomized study reported by Bottomley and Cunliffe.¹¹ Fifty-six subjects with acne vulgaris who failed previous treatment with at least 2 courses of oral antibiotic therapy with other agents received trimethoprim 300 mg twice daily used concurrently with topical clindamycin lotion 1% twice daily for at least 4 months. At the end of the initial 4-month treatment period, marked improvements in severity grading of both facial and truncal acne were observed. Twenty-one subjects continued the treatment regimen for 8 additional months without loss of efficacy.¹¹ Importantly, more current acne treatment recommendations suggest that prolonged antibiotic therapy should be used in combination with other agents, such as topical retinoids and benzoyl peroxide, the latter used to both augment efficacy and reduce the potential for emergence of less sensitive strains of *P. acnes*.^{12,13}

What is the mechanism of action of TMP-SMX?

Trimethoprim is a competitive inhibitor of dihydrofolate reductase and blocks the conversion of dihydrofolic acid into tetrahydrofolic acid. Sulfonamides, such as sulfamethoxazole, inhibit the conversion of paraaminobenzoic acid to dihydrofolic acid.³ Sulfonamides are bacteriostatic, but the combination of TMP-SMX is shown to be bacteriocidal.^{14,15}

Surface lipids, which play a vital role in the development of acne vulgaris, are derived from exogenous sources, sebaceous glands, epidermal cells, and keratin. In sebaceous-rich areas, such as the forehead, skin surface lipids are prominently made up of sebum, which plays an important role in the pathogenesis of acne vulgaris. Sebum is fractionated into free fatty acids, which are then synthesized into triglycerides and wax esters. Strauss and Pochi⁹ showed that when free fatty acids (fractionated from sebum) are injected into the skin, they produce an inflammatory response similar to that seen in acne vulgaris.

In a study of 17 subjects, Cotterill et al¹⁰ looked at the effect of TMP-SMX on the sebum excretion rate. TMP-SMX produced a marked decrease in sebum free fatty acids after 1 and 2 months of therapy while inversely increasing sebum triglycerides. However, TMP-SMX did not have any effect on the sebum excretion rate or on the levels of squalene, wax esters, or cholesterol.¹⁰

TMP-SMX reduces the free fatty acid content of the sebum⁴ and the titratable acidity of sebum, a

reliable indicator of free fatty acid content.² Neither trimethoprim nor sulfamethoxazole alone have any effect on the titratable acidity. It is possible that TMP-SMX acts by inhibiting the lipolytic activity of the surface bacteria.^{2,6}

Tetracyclines and TMP-SMX may possibly act on different sites in the pathway of sebum production because some patients treated unsuccessfully with tetracycline antibiotics improve when treated with TMP-SMX.² An alternative consideration may be differences in sensitivity of *P. acnes* strains to individual tetracyclines or TMP-SMX among different patients, especially in those patients previously treated with chronic administration of tetracycline.

What potential adverse reactions have been reported with the use of TMP-SMX?

Overall, TMP-SMX is well-tolerated by most patients in both adult and pediatric populations. Few adverse effects were reported in studies that evaluated TMP-SMX in the treatment of acne vulgaris. Ten days after starting TMP-SMX, Cotterill et al² noted one subject who developed a transient skin eruption that cleared spontaneously while the subject was still on the TMP-SMX therapy. In the study conducted by Macdonald et al,⁷ 2 subjects who were on the TMP-SMX therapy were noted to experience headaches/dizziness and a red macular eruption, respectively. No adverse effects were noted in the studies by Hersle⁴ and Jen,⁸ but it is important to note that the study sizes were small (43 subjects and 30 subjects, respectively).

A variety of side effects have been reported in patients treated with TMP-SMX for conditions other than acne vulgaris. The most commonly reported side effects are upper gastrointestinal disturbances (eg, nausea) and maculopapular skin eruptions; lower gastrointestinal symptoms such as diarrhea are less common.¹⁶⁻¹⁸ Rare anaphylactic reactions to TMP-SMX have been reported and are attributed to the sulfamethoxazole component because sulfonamides are recognized causes of hypersensitivity.¹⁶⁻¹⁸ Johnson et al¹⁹ reported 2 cases of anaphylactoid reactions in which patients presented with fever, hypotension, and bilateral pulmonary infiltrates within hours after receiving TMP-SMX. Sporadic cases of anaphylaxis caused by trimethoprim alone have been reported.²⁰

Cutaneous reactions have been reported with TMP-SMX therapy.¹⁷⁻²³ Symptoms usually begin within one week of starting the medication and resolve after the discontinuation of the drug. The most common cutaneous eruptions seen with TMP-SMX therapy are maculopapular or

morbilliform in nature, secondary to a type IV hypersensitivity reaction involving T lymphocytes. Cutaneous reaction rates to TMP-SMX are estimated to be approximately 4% to 5% in healthy patients and approximately 15% in patients infected with human immunodeficiency virus.¹⁷ Urticarial rash and/or pruritus can be seen with TMP-SMX therapy.^{21,22} Case reports have implicated TMP-SMX and trimethoprim as the cause of fixed drug eruptions.²³⁻²⁵ Exfoliative dermatitis also has been reported with TMP-SMX.²⁶

Sweet syndrome, or acute febrile neutrophilic dermatosis, is characterized by neutrophilia, fever, and painful erythematous plaques or nodules containing a rich neutrophilic dermal infiltrate. TMP-SMX has been reported as a cause of drug-induced Sweet syndrome. There may be an absence of neutrophilia in drug-induced Sweet syndrome.^{27,28}

Sulfonamide antibiotics, which include TMP-SMX because of its sulfamethoxazole component, have been reported in association with drug-induced hypersensitivity syndrome (DIHS), also known as drug rash with eosinophilia and systemic symptoms or DRESS.^{29,30} Predisposition to development of DIHS caused by aromatic amine sulfonamides appears to be based on genetically predisposed patterns of drug metabolism.³¹⁻³³ DIHS is characterized by a triad of fever, generalized exanthemalike skin eruption, and internal organ involvement (especially hepatotoxicity). Initial signs and symptoms of DIHS usually occur within 2 to 6 weeks after initiating the offending agent.³⁴ DIHS may be associated with considerable morbidity if the offending drug is not withdrawn.

Erythema multiforme, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) have been reported in association with TMP-SMX therapy and together account for most of the severe skin reactions associated with this drug. Chan et al²¹ reviewed medical records of patients diagnosed with erythema multiforme, SJS, or TEN who were discharged from Group Health Cooperative in Seattle, Washington, in a 14-year period (1972–1986). Drug-associated erythema multiforme, SJS, and TEN were noted in 9, 5, and 2 patients, respectively. TMP-SMX was implicated as the cause of SJS in one patient and TEN in another.²¹ The incidence of TEN in adults secondary to TMP-SMX exposure has been reported to be 2.6 per 100,000 exposures in the overall population and 8.4 cases per 100,000 exposures in patients with human immunodeficiency virus infection.³⁵

Although hematologic adverse reactions associated with the use of TMP-SMX are uncommon overall, a variety of potentially serious toxicities have been reported, including thrombocytopenia,

agranulocytosis, neutropenia, hypoprolthrombinemia, aplastic anemia, nonhemolytic anemia, and pure red cell aplasia.^{16,18,22,36-44} The incidence of any hematologic adverse reaction associated with the use of TMP-SMX has been reported to be one case per 18,000 prescriptions according to the Swedish adverse reaction reporting system.⁴³ TMP-SMX has been implicated as a definite or probable cause of thrombocytopenia,⁴² demonstrated in 10 of 515 cases reviewed in one report³⁶ and 26 of 309 cases in a second analysis.⁴⁴ The risk of agranulocytosis associated with TMP-SMX use has been reported to be 0.6 episodes per million patient days of drug intake, with an average treatment time of 13 days before confirmation of diagnosis.^{42,45} The overall risk of aplastic anemia associated with intake of sulfonamide antibiotics has been reported to be little to none.⁴² The incidence of aplastic anemia or pancytopenia occurring in association with the use of TMP-SMX was determined to be 1.1 cases per million daily patient doses. Nonhemolytic anemia, noted to occur in 0.1 cases per million daily patient doses, and pure red cell aplasia rarely have been reported in association with TMP-SMX use.^{42,43} It has been suggested that some TMP-SMX-induced blood dyscrasias, such as thrombocytopenia and neutropenia, may be more likely to occur in patients with megaloblastosis (as evidenced by an increase in mean corpuscular volume), in patients with underlying folic acid deficiency, or in patients receiving higher than usual doses of TMP-SMX.⁴² Although performance of complete blood cell counts has not been definitively recommended for all patients, it is a reasonable approach to evaluate patient status at baseline and periodically during the course of therapy.

Other rare side effects that have been reported in association with TMP-SMX use include drug fever, cholestatic hepatitis, phospholipidosis, and interstitial nephritis.^{16,46}

What are other important clinical considerations when prescribing TMP-SMX for acne vulgaris or other indications?

TMP-SMX, rated as pregnancy category C, is best avoided during pregnancy and is not recommended for use in the third trimester or in pediatric patients younger than 2 months; sulfamethoxazole can displace protein-bound bilirubin and lead to kernicterus in newborns.¹⁶ TMP-SMX also should be avoided in patients reporting a history of sulfonamide allergy or DIHS syndrome associated with sulfonamide use.³⁴ Cross-reactivity with nonaromatic amine-sulfonamide derivatives (eg, sulfonyleurea oral hypoglycemic agents,

thiazide diuretics, furosemide, acetazolamide) should not occur.⁴⁷ It has been suggested that sulfonamide antibiotic use should be avoided in first-degree relatives of patients experiencing DIHS secondary to TMP-SMX intake because of genetic metabolic predisposition.³¹⁻³⁴

Although a complete review of drug-drug interactions associated with TMP-SMX use is beyond the scope of this article, a few reported interactions with potential for major clinical significance are worthy of mention, especially because the use of TMP-SMX for the treatment of acne vulgaris is likely to be prolonged. TMP-SMX may augment the anticoagulant effect of warfarin.¹⁶ Hematologic toxicity, including severe reactions such as pancytopenia, have been reported in several patients on methotrexate therapy who have been administered TMP-SMX.^{16,42,48,49} This combination is best avoided.

It is recommended that the dose of TMP-SMX be reduced in patients with clinically noteworthy reduction in renal function.¹⁶

When should TMP-SMX be considered for the treatment of acne vulgaris?

Although TMP-SMX is not approved by the US Food and Drug Administration for the treatment of acne vulgaris, the drug's use for this condition is supported by multiple reports. Use of TMP-SMX in patients with acne vulgaris is not considered first-line therapy, rather it is reserved for patients refractory to other oral antibiotic regimens.^{16,50} In addition, concern regarding the potential for development of TEN supports using TMP-SMX as an alternative agent for acne treatment after conventional oral antibiotics, such as doxycycline or minocycline, have failed or are no longer effective. Anecdotally, the lead author has observed multiple selected patients with acne vulgaris who have been unresponsive to other oral antibiotics used in combination with a topical regimen and then respond favorably to TMP-SMX used in combination with the same topical program. It is important to consider that TMP-SMX is now commonly used to treat community-acquired methicillin-resistant *Staphylococcus aureus*, which is widespread in many communities across the United States. Therefore, it is prudent to use TMP-SMX judiciously in patients with acne vulgaris because treatment is likely to be prolonged for at least 2 to 3 months or longer, and efforts should be made to minimize the drug's overall exposure in the general population.

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