

The use of trimethoprim and sulfamethoxazole (TMP-SMX) in dermatology

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Abstract: We analyzed publications and articles in the PubMed database about the use of trimethoprim and sulfamethoxazole (TMP-SMX) in dermatology. Literature published in the English language, at least in the past two decades, was reviewed. Specific dermatologic indications for TMP-SMX are few but it is often used as the second- or third- line agent. TMP-SMX is used to treat cutaneous nocardiosis and *Aeromonas* infections. TMP-SMX is a treatment option for cat — scratch disease, granuloma inguinale, melioidosis and *Mycobacterium marinum/fortuitum* cutaneous infections. TMP-SMX is an alternate choice for treatment of pyodermas and lymphogranuloma venereum. TMP-SMX has been used to treat acne vulgaris in tetracycline and erythromycin — resistant patients. TMP-SMX is still the preferred empiric antibiotic for methicillin — resistant *Staphylococcus aureus* skin and soft tissue infection in HIV positive population. TMP-SMX is used in dermatology to treat various skin conditions and is one of the most commonly prescribed sulfonamide drugs. TMP-SMX as monotherapy is an effective treatment option in many diseases but due to drug resistance, a combination therapy-usually of two drugs-may be considered.

Key words: trimethoprim, sulfamethoxazole, co-trimoxazole, dermatological indications, cutaneous infections, combination therapy.

Introduction

Trimethoprim-sulfamethoxazole (TMP-SMX) or co-trimoxazole is a combined chemotherapeutic used in treatment of various bacterial, fungal and protozoal infections. Its manifold properties can find an implementation in various fields of medicine but there are not many publications regarding its dermatological use. TMP-SMX consists of two active pharmaceutical ingredients in a fixed dose ratio of one part trimethoprim to five parts sulfamethoxazole. The synergy between trimethoprim and sulfamethoxazole is effective in inhibition of

enzymes involved in the bacterial synthesis of tetrahydrofolic acid, which is essential in the bacterial nucleic acids synthesis. Sulfamethoxazole inhibits conversion of p-aminobenzoic acid (PABA) into dihydrofolic acid and trimethoprim blocks conversion of dihydrofolic acid into tetrafollic acid. Bacterial nucleic acid synthesis is selectively disrupted because bacteria are unable to transport exogenous folate through their cell walls [1]. Apart from its antimicrobial properties, there are some reports that TMP-SMX can present anti-inflammatory and immunomodulatory effects, enhancing the basic mechanism of action. Several studies show that co-trimoxazole can modulate both innate and adaptive immune cells facilitating antimicrobial pathways. Increased chemotaxis of neutrophils plays an important role in dermatological diseases mediated by neutrophils such as pyoderma gangrenosum. Increased productivity in phagocytosis and intracellular killing by macrophages improve bactericidal activity in infectious dermatoses, in which pathogens are not easily accessible for the immune system (mycobacterioses). There are some reports suggesting that TMP-SMX may reduce proliferation of lymphocytes. It's worth emphasizing that inhibition of lymphocytes T is crucial in preventing allograft rejection. However, there is some inconsistency between the authors of these studies therefore, further investigations should be provided [2].

Many aerobic bacteria are inhibited by TMP-SMX in vivo. Susceptible organisms comprise: Enterobacteriaceae, *Vibrio cholerae*, *Staphylococcus* spp. (including MRSA), *Streptococcus* spp. (excluding *Streptococcus pneumoniae*), *Haemophilus influenzae*, *Morganella morganii*, *Moraxella* spp., *Aeromonas hydrophila*, *Brucella* spp., *Burkholderia* spp., *Bordetella pertussis*, *Xanthomonas* (*Stenotrophomonas*) *maltophilia*, *Pseudomonas* spp. (excluding *Pseudomonas aeruginosa*), *Yersinia* spp., *P. jiroveci*, *Plasmodium* spp., *Nocardia* spp., *Listeria monocytogenes*, *Isospora belli*, *Cyclospora* spp., *Mycobacterium marinum* and *Mycobacterium fortuitum*. Co-trimoxazole exhibits minor activity against *S. Pneumoniae*, *N. meningitidis* and *Enterococcus* spp. It is vital to emphasize that *Mycoplasma* spp., *Rickettsia* spp., *Mycobacterium tuberculosis* and *Treponema pallidum* are resistant to TMP-SMX and should not be considered in treatment of these infections. The drug has also poor anaerobic activity.

Both TMP and SMX are well absorbed from the gastrointestinal tract. The half-lives of TMP and SMX in patients with normal renal function amount approximately to 11 ($t = 8.6-17$ h) and 9 ($t = 9-11$ h) hours, respectively. But along with progressive decrease of glomerular filtration rate (GFR), the half-life of TMP lengthens. In case of renal dysfunction, the half life of the major metabolite of SMX lengthens if GFR is 25 ml/min/1.73 m² or below. In elderly patients the clearance of SMX decreases. Regarding this information, in case of GFR > 30 ml/min we can prescribe the standard dose, if GFR is 15–30 ml/min a half of the standard dose should be considered and if GFR is below 15 ml/min it is not recommended to administer this drug.

TMP-SMX is widely distributed in body fluids and tissues such as: amniotic fluid and tissues of fetus, aqueous humor, cerebrospinal fluid, bile, secretions of the middle ear, sputum, synovial fluid, saliva, secretions of vagina, secretions of prostate and intracellular fluids.

The drug has the pregnancy category C and should not be administered in pregnant women unless the benefits of using this drug in mother are significantly higher than the risk of damage in fetus. Moreover, TMP-SMX is not recommended in breast feeding women, especially during the first 6 weeks of newborns' life [3].

TMP-SMX may prolong the prothrombin time of patients receiving concomitant warfarin by inhibiting metabolic clearance of warfarin. TMP-SMX can interfere with folic acid availability and the dosage of folic acid supplementation in patients taking methotrexate should be adjusted [1].

Common adverse effects of TMP-SMX are gastrointestinal and hypersensitivity reactions. Maculopapular eruptions are particularly common in patients with AIDS. Pustular eruptions, phototoxic eruptions, Sweet's syndrome, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported. Other adverse effects include aplastic anemia, neutropenia, agranulocytosis, thrombocytopenia, headache, fatigue, tremor, drug-induced fever, cholestatic hepatitis, crystalluria, nephrolithiasis and interstitial nephritis [1]. We should emphasize that these serious side effects have been reported but in practice, the events such as Sweet's syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis and blood dyscrasias are infrequent and TMP-SMX may be considered as a relatively safe chemotherapeutic [3].

Dermatologic indications for TMP-SMX

There are a few specific dermatologic indications for TMP-SMX but this chemotherapeutic is often used as the second — or third-line agent when conventional therapy is ineffective (Table 1).

Table 1

Disease	Treatment option — TMP/SMX	Reference number
Acne vulgaris	2,3-line drug, 80/400 mg q.d.	4
MRSA SSTIs	1-line drug, 160/800 mg b.i.d.	9
Nocardiosis	1-line drug 160/800 mg (+ DDS 100–200 mg) q.d.	11
Granuloma inguinale (donovanosis):	2-line drug, 160/800 mg b.i.d.	12
M. marinum infections	1,2-line drug (part of a multidrug therapy) 160/800 mg b.i.d.	13
M. fortuitum infections	2,3-line drug (part of a multidrug therapy) 160/800mg b.i.d.	14
Aeromonas infections	2-line drug 160/800 mg b.i.d. (+ ceftriaxon)	17
Melioidosis	1-line drug 320/1600 mg b.i.d. (eradication phase)	18, 19
Cat-scratch disease	6–8 mg/kg of TMP component (in complicated cases of CSD)	20, 21
Lymphogranuloma venereum	2-line drug 80/400 mg b.i.d.	22
Pyoderma gangrenosum	2-line drug 160/800 mg b.i.d.	23, 24

q.d. — quaque die

b.i.d. — bis in die

DDS — dapsone

TMP/SMX — trimethoprim/sulfamethoxazole

TMP-SMX can be used in treatment of acne vulgaris, perioral dermatitis and rosacea. In many instances, acne vulgaris treated with macrolide and tetracycline antibiotics has been shown to be ineffective. The reason for this treatment failure can be microbial resistance but some authorities postulate that the source of this inadequate response to conventional antibiotics may be related to seborrhea [4]. High sebum excretion rates can lead to reduced drug concentrations in pilosebaceous units preventing therapeutic action of antibiotics. A major analysis of 255 acne patients treated for 6 months with either oral erythromycin (1 g/day), minocycline (100 mg/day), oxytetracycline (1 g/day) or co-trimoxazole (400 mg/day) found out that a reduced clinical response in the presence of a high sebum excretion rate was associated with the usage of all these antibiotics; apart from trimethoprim. Therefore, trimethoprim can be useful in such instances [5]. It is also vital to emphasize that antibiotic resistance of *Propionibacterium acnes*, an important target in acne treatment, is increasing and cross-resistant patterns may occur e.g. erythromycin-resistant strains of *P. acnes* may have cross-resistance to trimethoprim-sulfamethoxazole [6].

TMP-SMX is an oral anti-staphylococcal agent that can be potent in treatment of skin and soft tissue infections (SSTIs) caused by methicillin-resistant *Staphylococcus aureus* (MRSA). In order to treat these infections, clinicians' frequent choices are antimicrobial agents such as trimethoprim - sulfamethoxazole, clindamycin, linezolid, doxycycline, rifampin, moxifloxacin and minocycline [7] but oral treatment of MRSA SSTIs still remains challenging due to discordance between in vitro susceptibility MRSA tests and in vivo effectiveness [8]. Recent studies show that patients with MRSA SSTIs treated with the higher dose of TMP-SMX (320/1.600 mg twice daily) for 7 to 15 days had a similar rate of clinical resolution as patients treated with the standard dose of TMP-SMX (160/800 mg twice daily) for 7 to 15 days. Therefore, the higher dose of TMP-SMX may not be necessary [9]. The lower dose of TMP-SMX may also improve the tolerance of this drug and minimize gastrointestinal side effects.

TMP-SMX is still a preferred empiric antibiotic for MRSA SSTIs in HIV positive population. Research has identified low CD4 counts, intravenous drug use, male to male sexual contacts, syphilis, end-stage renal disease and recent beta-lactam antibiotic use as risk factors for MRSA SSTIs in this population. We should emphasize that resistance rates to TMP-SMX in HIV positive population have increased but they remain lower than other antimicrobial agents [10].

Nocardiosis is an infectious disease, caused by Gram-positive bacilli of the order Actinomycetales, that presents as a primary cutaneous infection or as a disseminated disease. It mainly affects immunosuppressed individuals but can also affect immunocompetent patients. Cutaneous nocardiosis is an infection, which responds well to treatment with TMP-SMX, especially in case of a limited disease of relatively short duration. In severe, disseminated cases imipenem in monotherapy or in combination with amikacin should be instituted [11].

TMP-SMX is considered as an alternative regimen in treatment of granuloma inguinale (donovanosis): one double-strength (160 mg/800 mg) tablet orally twice a day for at least 3 weeks and until all the lesion have been completely healed. Granuloma inguinale is an endemic disease in some tropical areas such as India, Papua, New Guinea, the Caribbean, central Australia and southern Africa and recommended treatment is doxycycline 100 mg

orally twice a day for at least 3 weeks. In case of inadequate response to the treatment, the addition of aminoglycoside (e.g.: gentamicin 1 mg/kg IV every 8 hours) may be useful [12].

TMP-SMX can be used in treatment of infections caused by a non-tuberculous species of *Mycobacterium*. *Mycobacterium marinum* can be found in non-chlorinated water with worldwide prevalence. It is the most common atypical *Mycobacterium* that causes opportunistic infections in humans. Deep and superficial cutaneous infections may occur. In superficial cutaneous infections TMP-SMX is a treatment option as monotherapy. Others include: minocycline, clarithromycin and doxycycline but treatment often should be based on combination therapy due to multi-drug resistance of *Mycobacterium marinum* [13].

Mycobacterium fortuitum is a fast-growing species that can cause a skin infection after minor surgical procedures, when aseptic environment is not adequate. Rapid growing mycobacteria as a group are resistant to conventional antimycobacterial agents used to treat tuberculosis but are susceptible to several other antibiotics. Clarithromycin, ciprofloxacin, amikacin and cefoxitin are considered as first-line drugs. Alternative drugs include: doxycycline, imipenem, etambutol, co-trimoxazole and amoxicillin-clavulanic acid. The best treatment option has not been determined but a combined therapeutic regimen is usually needed [14].

Aeromonas bacteria may cause skin and soft tissue infections manifesting themselves as cellulitis, pustules, and furuncles. TMP-SMX is active against most species [15–17].

Melioidosis is an infection caused by the gram-negative bacterium *Burkholderia pseudomallei*. This disease is endemic in South-East Asia and North Australia with rare occurrence in temperate countries. Any organ, including the skin, can be involved in melioidosis and clinical presentation ranges from a localized infection to an acute inflammatory reaction, sepsis and death [18]. TMP-SMX is an effective regimen in the oral phase of melioidosis treatment. According to a recently published, double-blind, randomized controlled trial, TMP-SMX is as well effective as TMP-SMX plus doxycycline in the oral phase of melioidosis treatment. Therefore, this is a preferable option on the basis of patients' safety and tolerance [19].

Cat-scratch disease is generally not serious. Medical treatment is not usually needed. In complicated cases, the treatment with antibiotics such as trimethoprim-sulfamethoxazole, ciprofloxacin or azithromycin can be helpful. In AIDS patients and other people who have the weakened immune system, cat-scratch disease is more serious and the treatment with antibiotics, including gentamicin, is recommended [20, 21].

Lymphogranuloma venereum (LGV) is a sexually transmitted disease (STD) caused by the invasive serovars L1, L2 or L3 of *Chlamydia trachomatis*. LGV primary presents as a self-limited genital ulcer or papule but it can develop to major lesions. In advanced stages, it can be manifested as lymphadenitis, lymphangitis with tender inguinal and/or femoral lymphadenopathy. Rectal exposure to this pathogen may result in proctocolitis, which left untreated can lead to chronic, colorectal fistulas and strictures [12]. TMP-SMX can be a treatment option for lymphogranuloma venereum [1, 22] but 100 mg of doxycycline orally twice a day for 21 days is recommended as the first choice treatment [12].

Pyoderma gangrenosum manifests as deep ulcers, which can develop into chronic necrotic lesions. This disease can constitute a manifestation of paraneoplastic syndrome. Systemic treatment with corticosteroids and cyclosporine is documented in literature for a disseminated,

as well as for localized, disease and should be considered as the first-line therapy [23]. However, corticosteroids have a lot of side effects e.g.: glucose intolerance and high arterial pressure. According to the case report about relapsing facial pyoderma gangrenosum (malignant pyoderma), sulfa drugs and minocycline may be considered as an alternative therapy in treatment of pyoderma malignum but further results should be provided [24].

TMP-SMX may be considered as an option for topical treatment of uncomplicated and superficial skin infections such as impetigo and other skin infections caused by *S.aureus*. One study exhibits that *S. aureus* isolates have low resistant rates to topical TMP-SMX but there are not many publications confirming the effectiveness of topical treatment and further investigation should be provided [25].

Conclusions

TMP-SMX is a potent antimicrobial agent that has several advantages. It may be administered in penicillin - allergic patients. The standard dose of TMP-SMX (160/800 mg twice daily) is still effective with minimal gastrointestinal side effects. TMP-SMX is currently a therapeutic option in treatment of MRSA SSTIs. This chemotherapeutic pharmacokinetically penetrates adequately into tissue compartments including abscesses. It can be taken orally and intravenous administration should be limited to situations in which immediate treatment must be provided or a patient is unable to take this drug orally. Trimethoprim-sulfamethoxazole is used in dermatology to treat various skin conditions and is one of the most commonly prescribed sulfonamide drugs. Trimethoprim-sulfamethoxazole as monotherapy is an effective treatment option in many diseases but due to drug resistance, a combination therapy — usually of two drugs — may be considered.

Conflict of interest

None declared.

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