Clinical Commentary Review

Sulfonamide Hypersensitivity: Fact and Fiction

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Date of Original Release: September 1, 2019. Credit may be obtained for these courses until August 31, 2020.

Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

Accreditation/Provider Statements and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The AAAAI designates this journal-based CME activity for 1.00 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

List of Design Committee Members: David A. Khan, MD, Sandra R. Knowles, BScPhm, and Neil H. Shear, MD (authors); Michael Schatz, MD, MS (editor)

Learning objectives:

1. To discuss issues of cross-reactivity between sulfonamide antimicrobials and other sulfonamide drugs.

2. To be able to identify patients who may benefit from skin testing with sulfonamides.

3. To discuss the controversies in the effectiveness of desensitization versus rechallenge in patients with delayed reactions to sulfonamides.

Recognition of Commercial Support: This CME has not received external commercial support.

Disclosure of Relevant Financial Relationships with Commercial Interests: The authors declare that they have no relevant conflicts of interest. M. Schatz declares no relevant conflicts of interest.

Sulfonamide antimicrobials are commonly reported as causing drug allergy and have been implicated in a variety of hypersensitivity reactions including immediate IgE-mediated reactions, benign T-cell-mediated rashes, and severe cutaneous adverse reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms. Cross-reactivity is unlikely between sulfonamide antimicrobials and sulfonamide non-antimicrobials. In patients who develop reactions to a sulfonamide non-antimicrobial, there is no evidence to suggest that sulfonamide antimicrobials and other sulfonamide non-antimicrobials would cross-react. Although immediate skin testing can be performed in patients with histories of immediate reactions, they are infrequently positive and wane over time. Delayed skin testing including patch tests to sulfonamides is rarely positive. Drug challenges are a useful tool for patients with both immediate and delayed reactions to sulfonamides. The role of sulfamethoxazole desensitization is controversial as rates of hypersensitivity reactions are similar between desensitization and drug challenge. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:2116-23)

Key words: *Sulfonamide; Sulfa; Allergy; Hypersensitivity; Cross-reactivity; Skin test; Drug challenge*

Sulfonamide antimicrobials are a commonly reported allergy occurring in approximately 7% of patients exposed to this class.[1] Sulfonamides have been implicated in a variety of reactions including immediate IgE-mediated reactions, benign T-cell-mediated rashes and severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction eosinophilia systemic symptoms (DRESS). A concern regarding sulfonamide use is the potential for cross-reactivity among all drugs that contain a sulfonamide functional group.

DEFINITIONS

Sulfonamides are derivatives of *p*-aminobenzenesulfonamide (sulfanilamide). The term "sulfonamides" has been used to

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No funding was received for this work.
Conflicts of interest: The authors declare that they have no relevant conflicts of interest.
Received for publication May 14, 2019; revised May 26, 2019; accepted for publication May 29, 2019.

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2213-2198

https://doi.org/10.1016/j.jaip.2019.05.034

Abbreviations used
DRESS- Drug reaction with eosinophilia and systemic symptoms
FDE- Fixed drug eruption
PCP- Pneumocystis jirovecii *pneumonia*
RAST- Radioallergosorbent test
SCARs- Severe cutaneous adverse reactions
SJS- Stevens-Johnson syndrome
TEN- Toxic epidermal necrolysis
TMP-SMX- Trimethoprim-sulfamethoxazole

describe any compound with an SO_2NH_2 moiety, and can be divided into 2 groups: sulfonamide antimicrobials and non-antimicrobial sulfonamides.[2]

Sulfonamide antimicrobials contain an aromatic amine group at the N4 position, whereas most non-antimicrobial sulfonamides do not contain this group (Figure 1). The antiretrovirals fosamprenavir and amprenavir have an arylamine group at the N4 position. In addition, sulfonamide antimicrobials contain a 5- or 6-member aromatic heterocyclic ring with 1 or more nitrogens at the sulfonamide-N1 position; this substituted ring is not found with non-antimicrobial sulfonamides.

The term "sulfa" is a colloquial term used to describe patients with allergies to sulfonamide antimicrobials. Unfortunately, some patients may interpret this to mean that they are allergic to all drugs containing the "sulf-" prefix. Medications or other substances may contain sulfur, sulfites or bisulfate salts, including penicillins, cephalosporins, captopril, omeprazole, sodium metabisulfite, morphine sulfate, and ferrous sulfate. None of these medications are sulfonamides, and there is no risk of cross-sensitivity with sulfonamide antimicrobials.

IMMUNOPATHOLOGY

For IgE-mediated reactions, the N1-substitute and not the sulfonamide group has been found to have direct specificity to IgE antibodies. Specifically, 2 allergic epitopes have been identified: a 5- to 6-member aromatic heterocyclic ring with 1 or more nitrogens at the sulfonamide-N1 position, and the presence of a single methyl group on the carbon atom beta to the sulfonamide substitution.[3,4]

The metabolites of sulfonamide antimicrobials are hypothesized to be responsible for non—IgE-mediated reactions. In normal hosts, 45% to 70% of sulfamethoxazole, a representative sulfonamide antimicrobial, is acetylated at the N4 position to form N4-acetyl sulfamethoxazole, which is renally excreted as a nontoxic metabolite.[5] In contrast, an alternative pathway, which is more important in slow acetylators, involves cytochrome P450 isoenzyme 2C9.[6] The N4 hydroxylated metabolite can oxidize to a reactive nitroso compound or be reduced by reaction with glutathione.[7] The nitroso metabolite can cause direct cytotoxicity or bind to T cells to induce an immune response resulting in reactions such as SJS/TEN.[8] Non-antimicrobial sulfonamides do not contain the aromatic amine and therefore do not produce similar metabolites.

CROSS-REACTIVITY

Mechanisms of cross-reactivity

When a patient reacts to 2 different drugs, it is difficult to determine if this is the result of cross-reactivity or whether the patient has 2 independent reactions. Hypersensitivity reactions to 2 structurally similar drugs cannot be routinely assumed to be due to cross-reactivity.[9] For example, a retrospective cohort study determined that patients with allergic-like events after penicillin had an increased risk of events after either subsequent cephalosporins or sulfonamide antibiotics; however, cross-reactivity between penicillins and sulfonamide antibiotics cannot explain this increased risk.[10] In addition, in a related study among sulfonamide antibiotic—allergic patients, the risk of a subsequent allergic reaction was higher with penicillin than a sulfonamide nonantibiotic.[11]

There is limited evidence to support statements in manufacturers' product monographs regarding avoidance of sulfonamide non-antimicrobials for patients with a history of allergic reaction to sulfonamide antimicrobials. However, information found in product labeling regarding use in patients with a history of sulfonamide allergy is inconsistent ranging from no warning to a contraindication.[12,13] In addition, case reports have presented conflicting data, and there are no conclusive reports documenting cross-reactivity between sulfonamides and non-antimicrobial sulfonamides.[14]

The evidence indicates that cross-reactivity is unlikely between sulfonamide antimicrobials and sulfonamide non-antimicrobials. For sulfonamide antimicrobials, the sulfonamide moiety (ie, SO_2NH_2) itself does not trigger serious drug reactions such as DRESS or SJS/TEN, but rather the aromatic amine moiety is critical in the pathogenesis of these reactions. Non-antimicrobial sulfonamides (ie, nonaromatic amine sulfonamides) such as furosemide, celecoxib, and acetazolamide do not contain the aromatic amine moiety and would not be expected to clinically cross-react with sulfonamide antimicrobials (Table I).[15-17]

For IgE-mediated reactions with sulfonamide antimicrobials, the N1 substituent and not the sulfonamide group is important in determining specificity to antibodies. Nonantimicrobial sulfonamides, such as celecoxib, do not contain this chemical substituent and, therefore, would not be expected to cross-react with sulfonamide antimicrobials.

Drugs to avoid in patients who have reacted to sulfonamide antimicrobials

Cross-reactivity would be expected for sulfonamide antimicrobials as a class. For example, in a patient who develops DRESS from sulfamethoxazole-trimethoprim, it is reasonable to avoid all sulfonamide antimicrobials (regardless of route of administration) including sodium sulfacetamide (available as an ophthalmic product) and silver sulfadiazine (topical product). Patients should also avoid trimethoprim, as it is unknown whether this drug may have contributed or been responsible for the drug reaction. It may be prudent to recommend avoidance of drugs (or metabolite) containing an aromatic amine in patients who develop serious adverse reactions, including dapsone (a sulfone), fosamprenavir, darunavir, and sulfasalazine (Table II).[14,18] However, in HIV-infected patients with a history of trimethoprim-sulfamethoxazole hypersensitivity or intolerance, dapsone may be tolerated.[19] Sulfasalazine is metabolized to sulfapyridine, a sulfonamide antimicrobial, and would be expected to cross-react with other sulfonamide antimicrobials.

Cross-reactivity between non-antimicrobial sulfonamides

There is limited evidence regarding cross-reactivity with sulfonamide non-antimicrobials, such as furosemide or celecoxib. In

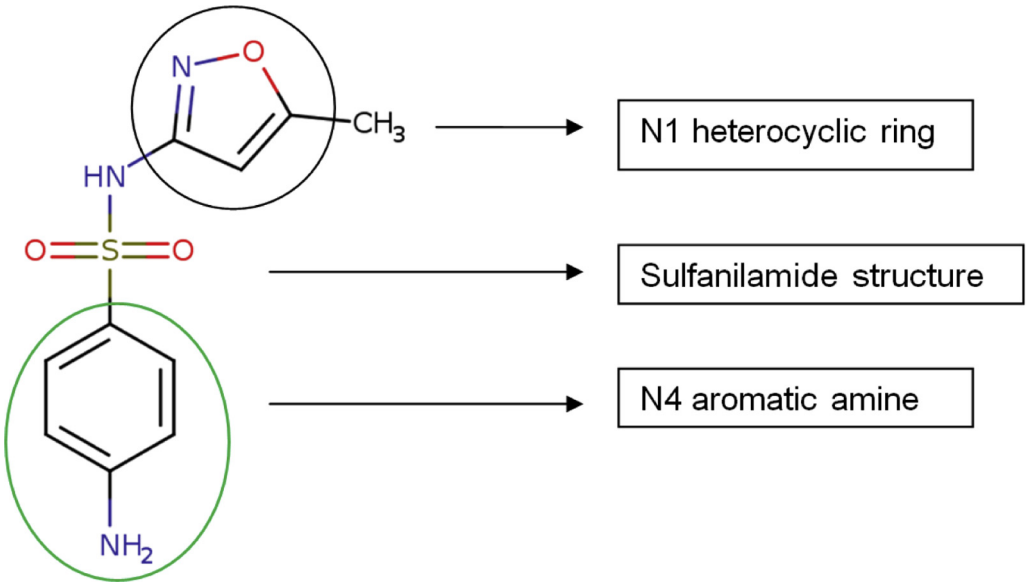

FIGURE 1. Sulfonamide structure.

patients who develop reactions to a sulfonamide non-antimicrobial, there is no evidence to suggest that sulfonamide antimicrobials and other sulfonamide non-antimicrobials would cross-react. For example, in a patient who develops a reaction to celecoxib, there are no data to indicate that other sulfonamide non-antimicrobials (such as furosemide) or sulfonamide antimicrobials need to be avoided. However, in patients with serious reactions (eg, SJS/TEN, DRESS), some clinicians may elect to avoid all sulfonamide medications; however, there is no evidence to support this strategy.

CLINICAL PRESENTATIONS

Immediate reactions

Although less common than other hypersensitivity reactions, immediate reactions due to IgE-mediated mechanisms can occur with sulfonamide antibiotics. Reactions can range from typical urticaria or angioedema to anaphylaxis, which in rare cases has led to fatalities.[20] Immediate reactions ranging from contact urticaria to anaphylaxis have even occurred with topical sulfamethoxazole eye drops.[21] In addition, trimethoprim itself can cause hypersensitivity reactions including anaphylaxis.[22]

Delayed reactions

Cutaneous reactions. Delayed reactions to sulfonamides can affect multiple organs, but cutaneous reactions are the most common. In a study from the Boston Collaborative Drug Surveillance Program involving 1121 hospitalized patients treated with trimethoprim-sulfamethoxazole (TMP-SMX), 38 patients (3.3%) had cutaneous reactions, which was slightly more common than gastrointestinal effects (3.2%).[23] These benign exanthema described as erythema, itch, and urticaria occurred within 72 hours in half of patients and 4 to 13 days later in the rest. All rashes cleared promptly with discontinuation of TMP-SMX. The occurrence of rash appears higher in patients treated with high-dose (≥4 TMP-SMX tablets/day) therapy.[24]

Maculopapular exanthemas are the most common form of cutaneous reaction to sulfonamides. A study of 191 Thai patients evaluated for cutaneous reactions to co-trimoxazole found 70 (36.6%) with maculopapular rashes.[25] Fixed drug eruptions (FDE) occurred in 22%, and urticaria in 12% with only 1% reported to have anaphylaxis. In this cohort, SCARs were identified in 22 patients (11.5%): 16 with SJS and 6 with DRESS. Other delayed cutaneous reactions associated with sulfamethoxazole include Sweet syndrome (acute febrile neutrophilic dermatosis), Baboon syndrome (a.k.a symmetrical drug-related intertriginous and flexural exanthema), psoriasiform dermatitis, acute generalized exanthematous pustulosis, and linear IgA bullous dermatosis.[26-30]

Although sulfonamide antibiotics are often considered as frequent culprits for causing SCAR, the data on this are somewhat mixed depending on the type of SCAR. The prospective RegiSCAR study on DRESS identified only 2 of 115 (1.7%) cases to be attributed to TMP-SMX.[31] Sulfasalazine was attributed in 7% of cases and dapsone in 3 cases. In contrast, data from the EuroSCAR study identified cotrimoxazole as a culprit in 6.3% of 379 cases, the most common antibiotic implicated.[32] A study of cutaneous adverse reactions from Australia identified "sulfur antimicrobials" in 8 of 29 (28%) cases of antibiotic-associated SCAR, which was similar to β-lactams.[33] A US study examining 5 years of data on 82 patients with TEN found that the most common causative drug was TMP-SMX accounting for 36.6% of all cases.[34] Two population-based cohort studies, one involving 232,390 people prescribed TMP-SMX in the United Kingdom and another US study of 107,689 people who filled 229,396 prescriptions for TMP-SMX, found a risk estimate of 1.7 and 2.8 per 100,000 respectively for skin reactions requiring hospitalization (erythema multiforme or SJS).[35,36] Finally, although a seasonal variation in TMP-SMX-induced SJS/TEN was suggested in 1 study, a larger study failed to find evidence for this.[37] Thus, sulfamethoxazole appears to be a relatively common culprit in cases of SJS/TEN, but not as frequent a cause of DRESS.

Extracutaneous reactions. Drug-induced liver injury to sulfonamides was reported frequently in case reports, especially

TABLE I. Drugs with no or weak evidence of cross-reactivity in patients with a history of a sulfonamide antimicrobial adverse reaction

Drug class	Drug or compound	Comments
Sulfonamide non-antimicrobials		
Alpha-blocker	Tamsulosin	Cross-reactivity is unlikely between sulfonamide antimicrobials and sulfonamide non-antimicrobials
Antiarrhythmics	Ibutilide, sotalol	
Anticonvulsants	Topiramate	
Carbonic anhydrase inhibitors	Acetazolamide, methazolamide, dorzolamide, brinzolamide	
COX-2 inhibitors	Celecoxib	
Diuretics, loop	Furosemide, bumetanide	
Sulfonylureas	Glimepiride, glyburide, gliclazide	
Diuretics, thiazide	Hydrochlorothiazide, chlorthalidone, indapamide, metolazone, diazoxide	
Triptans	Sumatriptan, naratriptan	
Other		
	Sulfur	No sulfonamide moiety and therefore no cross-reactivity
	Sulfate (eg, ferrous sulfate, magnesium sulfate)	
	Sulfites (eg, sodium metabisulfite)	

TABLE II. Drugs to avoid in patients with a history of a sulfonamide antimicrobial adverse reaction

Drug or compound	Comments
Sulfonamide antimicrobials	
• Sulfamethoxazole (oral/parenteral: cotrimoxazole, *Septra*)	Avoid all sulfonamide antimicrobials.
• Sulfasalazine (oral: *Salazopyrin*)	• Sulfasalazine should be avoided, as it is metabolized to sulfapyridine (a sulfonamide antimicrobial) and 5-ASA
• Sodium sulfacetamide (ophthalmic)	
• Silver sulfadiazine (topical: *Flamazine*)	
Other drugs	
• Dapsone (oral and topical)	• Conflicting information on cross-reactivity between dapsone and sulfonamide antimicrobials; suggest avoidance especially in patients with severe reactions.[19]
• Darunavir (oral: *Prezista*, *Prezcobix*)	• Fosamprenavir is a derivative of sulfanilamide and caution is recommended in patients with a history of sulfonamide antimicrobial allergy.
• Fosamprenavir (oral: *Telzir*)	• Although reports suggest that many patients with a sulfonamide allergy may tolerate darunavir, caution is advised when initiating therapy with darunavir[18]
Trimethoprim (oral)	• Trimethoprim should be avoided in patients who reacted to sulfamethoxazole-trimethoprim, as it is unknown which component was the causative agent

ASA, 5-Aminosalicylic acid.

before 1947.[38] TMP-SMX remains one of the most common single causative agents of drug-induced liver injury.[39] Most cases occur within 2 to 12 days of initiation of therapy with the most typical pattern of injury being a mixed hepatocellular cholestasis.[40] Some cases may be manifestations of DRESS. Rare cases of hepatotoxicity and concomitant hemorrhagic pancreatitis have also been reported.[41] Gastrointestinal complaints are common with most antibiotics including sulfamethoxazole, but eosinophilic gastroenteritis has been rarely reported.[42] Hematologic abnormalities including neutropenia, leukopenia, thrombocytopenia, and pancytopenia have also been reported with a risk estimate for reactions requiring hospitalization to range from 0.9 to 5.6/100,000.[36] Renal impairment has previously been reported to be rare with TMP-SMX, but a study of 573 middle-aged veterans treated with TMP-SMX found that 11.2% had evidence of acute kidney injury.[43] Most cases were asymptomatic and reversible on discontinuation of therapy but one did require dialysis. The mechanism was unclear with little evidence for acute interstitial nephritis. TMP-SMX is the most common antibiotic causing aseptic meningitis and has been the subject of a recent literature review in 2014 where the authors identified 41 cases with the first case reported in 1983.[44] Most reactions started hours to several days after initiation of therapy with headache and neck stiffness. The majority had fever and 50%

TABLE III. Diagnostic and management procedures for patients with reactions to sulfamethoxazole

Procedure	History of immediate reaction	History of delayed reaction
Prick/intradermal	Rarely helpful Recommend for anaphylaxis	Rarely helpful
Patch	Not indicated	Rarely helpful
Open application	Not indicated	Consider for fixed drug eruption
1- to 2-step challenge	Recommend but limited evidence	Recommend full dose challenge*
Multistep desensitization/challenge	Recommend rapid 5- to 6-h protocol for those with anaphylaxis	Consider 6-h protocol, but full dose challenge may be equally effective*

SCARs, Severe cutaneous adverse reactions.
*Drug challenges/desensitizations are contraindicated in patients with histories concerning for SCARs or noncutaneous, organ-specific reactions (eg, drug-induced liver injury).

had nausea and vomiting. Most patients became afebrile and had resolution of headache within 2 to 3 days of stopping therapy. The mechanism of this drug-induced aseptic meningitis remains unclear.

Reactions in HIV-positive patients. Co-trimoxazole remains the standard of care for prevention of *Pneumocystis jirovecii* pneumonia (PCP) in patients with HIV. A high frequency of hypersensitivity reactions to cotrimoxazole were initially identified in the 1980s from 2 small series totaling 54 AIDS patients who developed cutaneous reactions in 33% to 50% of treated patients.[45,46] A larger prospective study in 2002 followed 136 HIV-positive patients treated with sulfonamides for PCP or cerebral toxoplasmosis.[47] Forty-eight (35%) developed a drug eruption after a median of 9 days. The vast majority (85%) had maculopapular exanthema but 3 cases had severe cutaneous eruptions including 1 case of SJS. This study did not find an association with slow acetylation genotype or phenotype. Furthermore, concomitant corticosteroids did not appear to have a protective effect. Pharmacogenomic studies of 136 HIV-positive patients including 53 cases of hypersensitivity reactions (5 who had SJS) were unable to identify any polymorphisms in biologically plausible genes in the major histocompatibility complex to explain these reactions.[48]

DIAGNOSIS

Skin and *in vitro* testing

Skin testing has been performed in patients with immediate reactions. The most detailed study was performed by Gruchalla and Sullivan,[49] who developed a sulfamethoxazole poly-L-tyrosine conjugate to use for skin testing. They identified 34 patients with immediate reactions and found that 29% had positive skin tests. They also followed 3 patients with serial skin tests, and interestingly 2 of the 3 lost their skin test reactivity in less than a year, suggesting that IgE does wane over time. They also followed sulfamethoxazole-IgE by radioallergosorbent tests (RAST) in these same 3 individuals. RAST were positive in only 2 of the 3 patients and became negative within months of the reaction, despite the skin test reactivity persisting. This sulfamethoxazole poly-L-tyrosine conjugate has never been commercially available; however, skin testing with native trimethoprim-sulfamethoxazole can be performed with a nonirritating intradermal concentration using a 1:100 dilution of the 16 mg/80 mg per mL concentration of the intravenous formulation of co-trimoxazole.[50] For patients with histories of immediate reactions to TMP/SMX, the authors typically perform skin tests only in those with convincing histories of anaphylaxis.

The use of delayed prick and intradermal skin tests has been infrequently reported in the evaluation of delayed sulfamethoxazole reactions. Belchi-Hernandez et al[51] reported on performing delayed prick and intradermal skin tests in 33 patients with HIV who underwent an 11-day TMP-SMX desensitization protocol. All skin tests were negative despite the fact that 14 of 33 developed objective cutaneous reactions during the desensitization, suggesting that in the HIV population this testing is of limited value. For typical TMP-SMX exanthema, patch testing has also been infrequently reported. Gompels et al[52] performed patch tests in 4 HIV-positive patients who reacted after a TMP-SMX desensitization and all were negative. Kardaun et al[53] reported an HIV-positive patient with negative TMP-SMX patch tests who after desensitization developed fever and nonpruritic flare up of prior patch test sites. Patch testing has also been evaluated in fixed drug eruptions to TMP-SMX. Although Lee[54] reported 3 of 3 FDE patients with positive patch tests, a larger study by Ozkaya-Bayazit et al[55] performed patch testing following tape stripping in 27 patients with FDE from TMP-SMX and all were negative. However, open application with TMP-SMX in dimethyl sulfoxide was positive in 25 of 27 cases, suggesting that this method is better for evaluation of FDE. Finally, a single case of a positive sulfamethoxazole patch test (only in previously affected skin) was reported in a patient with TEN.[56] Overall, the results of both delayed prick/intradermal and patch testing for evaluating delayed TMP-SMX reactions are disappointing, and the authors do not routinely use these in diagnostic evaluations (Table III). Furthermore, various *in vitro* assays have been used for evaluation of both immediate and delayed reactions to TMP-SMX but are not recommended for evaluation.[57]

Abbreviated challenges

There is minimal information on abbreviated drug challenges with sulfonamides, especially in non−HIV-positive patients. A position statement from the European Academy of Allergy and Clinical Immunology states that drug provocation tests for sulfonamides in non−HIV-positive patients are difficult to justify as they are considered "mostly obsolete."[58] The authors have successfully performed 1- to 2-step challenges in several patients with remote cutaneous reactions to TMP-SMX who are in need of acute therapy or for antimicrobial prophylaxis.

MANAGEMENT OF PATIENTS WITH A HISTORY OF SULFONAMIDE HYPERSENSITIVITY

Multistep challenge/desensitization

More than 20 desensitization or multistep graded challenge protocols have been published, the vast majority used in patients

with HIV who are in need of prophylaxis with TMP-SMX.[59] Most patients have histories of delayed exanthema, and despite the large variability in protocols, most are successful in allowing patients to tolerate reintroduction of TMP-SMX. Most protocols use an up-dosing regimen over several days; however, Demoly et al[60] used a 6-hour protocol in 44 patients with a 95% success rate of tolerance of TMP-SMX after 10 months. Similar techniques have been described in non−HIV-infected patients with the largest report from Pyle et al.[61-63] They used multiple separate protocols in 72 non−HIV-positive patients ranging from a 6-step protocol with up-dosing every 15 minutes to a 10-day protocol with daily up-dosing. All protocols had similar success rates (98% to 93%). A single case report noted the successful use of a 10-day desensitization protocol for a patient with a history of FDE to TMP-SMX.[64] Although widely considered a contraindication to desensitization, Douglas et al[65] successfully used an 8-day desensitization protocol in 2 patients with histories of SJS to TMP-SMX.

Desensitization for anaphylactic reactions to TMP-SMX has rarely been reported. Gluckstein and Ruskin[66] used a rapid 5-hour desensitization protocol for patients with HIV that included 8 patients who had "anaphylactoid" reactions (including hypotension in 5 patients) that occurred within minutes of prior TMP-SMX dosing. This protocol was successful in the majority, and no patient had anaphylaxis during the desensitization.

Full dose challenge versus desensitization

Whether any of these protocols truly induce drug tolerance (desensitize) is not known. Three studies have compared rechallenge to a typical graded challenge/desensitization. Bonfanti et al[67] performed a randomized, open label, multicenter study in Italy comparing full-dose rechallenge with a previously published 2-day 40-step desensitization. Success rates were not statistically different between the 2 groups; rechallenge was successful in 18 of 25 patients (72%) versus 27 of 34 (79%) in the desensitization group. A smaller Brazilian study randomized 18 patients to full dose challenge versus a several day dose escalation and found that 40% of each group had mild reactions.[68] Finally, Leoung et al[69] performed the largest study on this issue, a randomized, double blind controlled, multicenter US trial comparing full dose rechallenge with a 6-day dose-escalation regimen. The duration of the blinded period was 6 days, and afterward both groups were treated open label and followed for 6 months. There was no difference at 6 days in tolerability of TMP-SMX in either group: 86 of 94 (91.5%) full dose challenge versus 91 of 97 (93.8%) in the dose-escalation group. However, when followed at 6 months, a higher percentage of patients were continuing therapy in the dose-escalation arm (80%) versus the full dose challenge group (62.8%). However, the occurrence of rashes was the same for both groups in the open label maintenance phase, yet the full dose challenge group had more frequent headaches and fever leading to drug discontinuation. A Cochrane review of these 3 studies concluded that desensitization resulted in fewer discontinuations than rechallenge.[70] However, from an allergist's perspective, it would appear that both groups had a similar rate of hypersensitivity reactions and this clearly questions whether these "desensitization" procedures are simply prolonged drug challenges that likely are not required for most patients. On the basis of the evidence, the authors recommend full dose rechallenge in patients with typical histories of benign exanthema to sulfonamides as an effective and straightforward approach for the majority of patients.

Treating through reactions

Because of concerns for SJS/TEN, most allergists are very reluctant to consider treating through a benign rash in a patient on TMP-SMX. However, many of the aforementioned challenge/desensitization protocols used antihistamines to treat benign rashes that occurred and there are cases that without desensitization have used a "treat through" approach with antihistamines in patients on TMP-SMX with rash and fever.[71] If this approach is used, patients should be monitored closely for evidence of progression into a more severe drug hypersensitivity syndrome.

KNOWLEDGE GAPS

Sulfonamide hypersensitivity remains a common problem. Current diagnostic tests such as skin and *in vitro* tests lack adequate precision, and there is a need for better diagnostic methods. There is a preponderance of literature on the use of desensitization protocols; however, more simplified challenge procedures are more straightforward and obviate the need for repeating these procedures with gaps in therapy. Further studies, particularly in non−HIV-positive patients, are needed.

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