

Sulfasalazine-Related Hypersensitivity Reactions in Patients With Rheumatic Diseases

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Background: Sulfasalazine (SSZ), which has an arylamine sulfonamide structure, is an anti-inflammatory drug used in the treatment of many rheumatic diseases. Various adverse effects have been reported related to SSZ. In the present study, we aimed to define the frequency of SSZ-related hypersensitivity reaction in patients with rheumatoid arthritis and ankylosing spondylitis.

Methods: A total of 136 patients were included in this study. During follow-ups, reaction type, reaction duration, and drug doses were recorded in patients who developed hypersensitivity reactions. Drugs were discontinued in patients who developed reactions, and they were treated with antihistaminics and/or corticosteroids, according to requirements. Drug provocation tests with the drugs and aminosalicic acid were performed in patients with negative skin prick test individually.

Results: A total of 136 patients, with ages ranging from 19 to 71 years (mean, 41.97 [SD, 12.04] years), were included in the study. Hypersensitivity reactions according to the drug provocation test were found against SSZ in 12 patients (8.8%). The SSZ-related hypersensitivity reaction types were urticaria in 7 patients, urticaria and angioedema in 4 patients, and pruritus in 1 patient.

Conclusions: Sulfasalazine is widely used by rheumatologists in the treatment of rheumatic diseases. Whereas the frequency of sulfonamide-related hypersensitivity reactions was reported as 3.0% in the population, we detected hypersensitivity reactions to be 8.8% with SSZ usage in rheumatic diseases.

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Sulfonamide-related drug allergic reactions are commonly encountered, and the incidence has been reported as 3% in the general population.¹ Sulfonamides are divided into 2 groups according to their structures as antibiotic sulfonamides and non-antibiotic sulfonamides. Antibiotic sulfonamides (sulfamethoxazole [SMX], sulfadiazine, sulfacetamide, sulfisoxazole) have an arylamine structure, and it is believed that this arylamine part is the main part responsible for hypersensitivity. While antiretroviral (amprenavir, fosampranavir) and anti-inflammatory (sulfasalazine [SSZ]) drugs from the nonantibiotic sulfonamide family have an arylamine structure, other compounds from the same family such as diuretics, antidiabetics, and analgesics are not arylamine based. Cross-reaction risk is lower between sulfonamide antibiotics and nonantibiotics because they are structurally different.²

Sulfasalazine, which has an arylamine sulfonamide structure, is an anti-inflammatory drug used in the treatment of many rheumatic diseases. Following its oral administration as a prodrug, it is dissolved into 5-aminosalicylic acid and sulfapyridine by bacterial azoreductase in the colon.³ Sulfasalazine may cause severe, even

fatal hypersensitivity reactions, and hypersensitivity reactions are mainly related to sulfapyridine structure.²

In the present study, we aimed to define the frequency of SSZ-related hypersensitivity reaction in patients with rheumatoid arthritis (RA) and ankylosing spondylitis (AS), who were newly diagnosed and had recently started SSZ treatment, and to investigate the effects of concomitant use of other immunosuppressive treatments on hypersensitivity reactions.

MATERIALS AND METHODS

This study has been approved by the Local Ethics Committee of Adnan Menderes University School of Medicine. This is a retrospective study. A total of 136 patients (106 female and 30 male patients) who were seen at our clinic between January 2015 and July 2015 newly diagnosed with RA or AS and received SSZ containing treatment were included in this present study. Patients who had previous drug allergy history or any allergic disease history were excluded from the study. Of the patients, 84 patients had RA, and 52 patients had AS. The patients were informed about possible adverse reactions and monitored. Sulfasalazine treatment was given as 1 g/d in the first week, 1.5 g/d in the second week, and 2 g/d in the third and following weeks; methotrexate (MTX) treatment at 15 mg/wk; and hydroxychloroquine (HCQ) 200 mg/d. Depending on active joint complaints, low- to moderate-dose corticosteroid (CS) and/or nonsteroidal anti-inflammatory drugs (NSAIDs) were added to the treatment.

During follow-ups, reaction type, reaction duration, and drug doses were recorded in patients who developed hypersensitivity reactions. Drugs were discontinued in patients who developed reactions, and they were treated with antihistaminics and/or CSs, according to requirements. A skin prick test was performed 4 weeks after reactions with usage drugs and aminosalicic acid. Skin prick tests were performed after preparing the drug, which had no injectable form but only tablet form, by crushing the tablets into powder. The dry powder was then dissolved in saline solution and administered. Drug provocation tests (DPTs) with the drugs and aminosalicic acid were performed in patients with negative skin prick test individually. The drug provocation test was administered orally for all of the drugs. Before the skin prick test and DPT, verbal and written patient consents were obtained, and physical examinations were performed. Drug provocation tests were performed under supervision of nurses and physicians by hospitalization. The DPT was administered at 1-hour intervals as follows: test was started at 1/10 of initial dose of the drug, and then as no reaction was observed, the dose was increased sequentially as 1/4, 3/4, and full dose. Patients were reevaluated before each new dose, and then they were given the next dose. The patients were monitored for at least 4 hours following the DPT. Provocation was performed once a week, and in patients without any known reaction, treatment was continued for a week, with the provocation test for the other drug performed in the second week. Therefore, drugs were added to the treatment after 1-week provocation tests. In patients who developed hypersensitivity, other concomitantly

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used immunosuppressants were also examined to determine whether they had effects on reactions.

Statistical Analysis

SPSS 18.0 software (SPSS Inc, Chicago, IL) was used for statistical evaluation of data. The collected data are presented as mean (SD) and percentage. Comparison of qualitative data was performed using Fisher exact tests.

RESULTS

A total of 136 patients (106 female and 30 male patients), with ages ranging from 19 to 71 (mean, 41.97 [SD, 12.04] years), were included in the study. Of all patients, 84 patients had RA, and 52 patients had AS. Hypersensitivity reaction was observed in 15 (11.02%) of 136 patients. We observed urticaria in 8 patients, urticaria and angioedema in 2 patients, and pruritus in 5 patients. Reactions were mild to moderate in intensity, and no serious reaction was observed. Skin prick test was primarily performed on patients who developed hypersensitivity reactions. As all of the patients had negative skin prick tests, drug provocation test was performed on all of them. According to the results of DPT, hypersensitivity reaction was related in 1 (1.7%) of 58 patients to HCQ, 2 (3.3%) of 60 patients to NSAIDs, and 12 (8.8%) of 136 patients to SSZ. Hypersensitivity reactions according to the DPT were against HCQ in 1 (1.7%) of 58 patients, NSAIDs in 2 (3.3%) of 60 patients, and SSZ in 12 patients (8.8%). Hypersensitivity reactions observed were similar to previous reactions.

There was no statistically significant difference in patients who developed SSZ-related hypersensitivity reactions with regard to age and sex, respectively ($P = 0.894$, $P = 0.137$).

According to patient groups, 8.3% of RA patients (7/84) and 9.6% of AS patients (5/52) had SSZ-related hypersensitivity. There was no significant difference in the frequency of the reaction between patient groups ($P = 0.767$).

Sulfasalazine-related hypersensitivity reaction types were observed as urticaria in 7 patients, urticaria and angioedema in 4 patients, and pruritus in 1 patient.

The dose of SSZ was 2 g/d for 10 patients and 1 g/d for 2 patients when the reaction occurred. The reaction occurred on the sixth day in 1 patient, on the seventh day in 1 patient, and on the 15th day or later in 10 patients (Table 1).

The effects of concomitantly used immunosuppressive drugs with SSZ were examined on hypersensitivity reaction. It was observed that concomitant use of MTX, HCQ, CS, and NSAIDs had no effects on SSZ-related hypersensitivity reaction ($P = 0.283$, $P = 0.943$, $P = 0.789$, $P = 0.765$) (Table 2).

DISCUSSION

Sulfonamide antibiotics differ from other sulfonamides by carrying an arylamine group (arylamine) at N4 position and a variable ring at N1 position. Various allergic reactions observed with sulfonamide antibiotics develop against N4 arylamine and N1 ring, which determines the type of antibiotic. Therefore, sulfonamide antibiotics are also named sulfonamides.⁴⁻⁷

Sulfasalazine has been used effectively in the treatment of RA, AS, and inflammatory bowel diseases for many years. It is dissolved into its 2 major metabolites, 5-aminosalicylic acid and sulfapyridine, by colonic flora in the colon. Sulfapyridine is absorbed rapidly and metabolized in the liver by acetylation. Sulfapyridine is included in the sulfanilamide group. Because it contains arylamine structure, cross reaction may develop; thus, patients with SMX allergy must avoid using SSZ, or patients with SSZ allergy must avoid using SMX.² None of the patients included in our study had a history of the drug allergy.

Sulfonilamide hypersensitivity reactions can develop as immunoglobulin E mediated and rarely as immunoglobulin G mediated or as reactions mediated by different T-cell types.⁸ Although rash is commonly encountered, serious cell-mediated reactions such as drug rash with eosinophilia and systemic symptoms, Stevens-Johnson syndrome, or toxic epidermal necrolysis may also be encountered.^{5,8}

Various adverse effects have been reported related to SSZ, and it has been observed that adverse effects are generally dose dependent and mild. Therefore, it is recommended to initiate the drug at low dose and increase gradually. Hypersensitivity reactions are not common, but they may be life-threatening.^{9,10} Sulfapyridine is the main molecule responsible in hypersensitivity reactions because of its arylamine structure. Although sulfonamide-related hypersensitivity reactions have been reported as 3% in the literature, we detected this ratio as 8.8% in our study by the use of SSZ.

In the literature, SSZ-related hypersensitivity reactions have been reported more commonly as rash and cell-mediated delayed type of hypersensitivity reactions.¹¹⁻¹⁴

TABLE 1. Clinical and Demographic Characteristics of Patients Who Have Developed SSZ-Related Hypersensitivity Reaction

Patient No.	Angioedema	Urticaria	Pruritus	Reaction Dose, g/d	Reaction Day	Sex	Disease
1	—	+	—	2	16	M	AS
2	—	+	—	2	15	F	RA
3	—	+	—	2	15	F	RA
4	+	+	—	1	6	F	RA
5	—	—	+	2	15	M	AS
6	+	+	—	2	15	M	AS
7	—	+	—	2	17	M	RA
8	—	+	—	2	15	F	AS
9	—	+	—	1	7	F	AS
10	+	+	—	2	20	F	RA
11	+	+	—	2	15	F	RA
12	—	+	—	2	15	M	RA

F indicates female; M, male.

TABLE 2. Concomitantly Used Immunosuppressive Drugs and Dosage in Patients Who Had SSZ-Related Hypersensitivity Reactions

Patient No.	MTX, mg/wk	HCQ, mg/d	Methylprednisolone, mg/d	NSAIDs, mg/d
1	—	—	—	75 (Indomethacin)
2	—	200	8	—
3	15	200	8	—
4	15	200	12	—
5	—	—	—	100 (Indomethacin)
6	—	—	—	400 (Ibuprofen)
7	15	—	—	100 (Diclofenac)
8	—	—	—	75 (Indomethacin)
9	—	—	—	75 (Indomethacin)
10	15	200	8	—
11	—	200	4	—
12	—	—	—	800 (Ibuprofen)

We observed urticaria and/or angioedema (type 1 reaction) in 11 of 12 patients who developed allergic reaction associated with SSZ. These reactions occurred on the sixth and seventh days in 2 patients receiving 1-g/d dose. Ten patients developed a reaction following the dosage increase to 2 g/d in the 15th day or later. Pruritus was observed at 2-g/d dose in 1 patient. These results suggested that the hypersensitivity reactions that developed in patients might be dose dependent.

No difference in age or sex was observed among patients with reactions. In addition, no correlation was observed in patients with reactions between underlying disease type and the reaction.

In patients with resistance to chronic autoimmune urticaria, efficiency of immunosuppressive treatments such as SSZ, MTX, and HCQ was shown in previous studies.^{15–20} Corticosteroids are used in acute attacks of urticaria with great efficiency.²¹ However, we observed in our study that allergic acute urticaria/angioedema might be developed at a rate of 8.8% using SSZ, which was shown to be one of the effective drugs used in chronic autoimmune urticaria treatment. Concomitant usage of HCQ, MTX, or low to moderate dose of CSs did not affect development of type 1 reactions.

Sulfasalazine-related delayed-type reactions are reported as case presentations in the literature. However, we did not observe any delayed-type hypersensitivity reactions in our study, and we considered that they might be prevented by concomitantly used immunosuppressive treatments and CS.

In conclusion, SSZ-related reactions are most commonly type 1 hypersensitivity reactions, and it is clinically urticaria. Reaction seems to be related to dose, and it is developed frequently at 2 g. Dose-related reactions are more commonly observed on the 14th day and later. Concomitantly used immunosuppressive treatments (MTX, HCQ, CS) also have no effect on the development of this type of reaction.

Sulfasalazine is widely used in the treatment of rheumatic diseases by rheumatologists. Such reactions might be ignored as alternative treatment options are available in the case of type 1 reactions. However, as there is a potential cross-reaction risk with sulfonamide group antibiotics, these types of patients should be determined. Patients who have SSZ-related allergic reactions should be advised to avoid sulfanilamide antibiotics such as SMX.

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