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Complications of sulfasalazine therapy in rheumatology practice

ABSTRACT

Sulfasalazine is a drug commonly used in rheumatology and gastrology, unfortunately, up to 50% of patients report side effects during therapy. Most of them have a mild course and their significant factor is the genetically determined metabolism of the drug, which leads to the accumulation of the metabolite — sulfapyridine, responsible for toxic symptoms. Serious side effects are less frequent and may have varied pathomechanisms. Usually, they are difficult to recognize because in the early period they can imitate the course of many inflammatory and systemic diseases, therefore their appearance is not immediately associated with the patient's intake of sulfasalazine, which may delay proper management and be fatal for the patient. This work aimed to present the serious complications that were observed in patients treated with sulfasalazine, i.e. drug rash with eosinophilia and systemic symptoms (DRESS syndrome), febrile neutropenia and severe nephrotic syndrome. Diagnostic and therapeutic difficulties in individual disease entities were discussed.

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KEY WORDS: sulfasalazine; drug rash; febrile neutropenia; nephrotic syndrome

INTRODUCTION

Sulphasalazine is a drug commonly used in rheumatology and gastrology. It is a sulphonamide derivative that combines 5-aminosalicylic acid and sulphapyridine. It has bacteriostatic, anti-inflammatory and immunosuppressive effects. It treats ulcerative colitis, Crohn's disease, spondyloarthropathies, juvenile idiopathic arthritis (JIA) and rheumatoid arthritis (RA). In approximately 25–50% of patients, the drug causes mild side effects, the predominant ones being dyspeptic complaints, increased liver enzymes, decreased appetite, leucopenia, headache and rash. Potentially life-threatening complications following sulphasalazine use include DRESS syndrome, severe nephrotic syndrome, neutropenic fever, toxic epidermal necrolysis, Stevens-Johnson syndrome, facial oedema, pancreatitis and pseudomembranous colitis, among others.

Serious adverse reactions are less common, so they are not immediately linked to the patient's intake of sulphasalazine, which can delay appropriate management and be tragic for the patient [1–3].

Our study aims to present the severe complications we observed in patients treated with sulphasalazine, i.e. drug rash with eosinophilia and systemic symptoms (DRESS syndrome), neutropenic fever and severe nephrotic syndrome.

DRUG RUSH WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS) SYNDROME

A female patient, aged 18, with recurrent bilateral uveitis of unknown origin (evaluation excluded ophthalmic causes, spondyloarthropathy (SpA), systemic connective tissue diseases, sarcoidosis, brucellosis, TINU syndrome, bacterial and viral infections, including viral hepatitis) treated with both topical and systemic glucocorticosteroids. In addition, history of recurrent palatine tonsillitis and allergy to Biseptol (minor rash). Due to

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the failure of previous therapy, sulphasalazine was included in the treatment at an initial dose of 1 g/day. The dose was increased after 12 days to 2 g/day. Two weeks after starting sulphasalazine treatment, the patient developed a micropapular, itchy, confluent rash involving the face, trunk and extremities, slight facial oedema with cervical lymphadenopathy, fever up to 39°C and concomitant weakness. The patient also reported pain in the knee and wrist joints but without oedema or stiffness. Physical examination revealed no signs of arthritis. The patient was admitted urgently to the rheumatology department. Laboratory tests showed the following abnormalities: leucopenia (WBC 3200/μL), eosinophils 600/μL, slightly reduced platelet count (PLT = 140 000/μL), biochemical signs of liver damage (ALT = 256; AST = 157; GGTP = 181; ALP = 152 IU/mL), low iron concentration (7.8 μg/L), increased ferritin concentration (270 μg/l) and CRP = 39 mg/L. Ultrasound imaging showed multiple enlarged, reactive cervical lymphadenopathy (up to 37 mm) and an enlarged liver (160 mm). The differential diagnosis excluded, among other things, bacterial and viral infections, including viral hepatitis and systemic connective tissue diseases.

Based on the history, the skin and organ lesions, the investigations and the criteria proposed by the Registry of Severe Cutaneous Adverse Reactions (RegiSCAR), the patient was diagnosed with probable DRESS during sulphasalazine therapy (Tab. 1).

Sulphasalazine was discontinued, methylprednisolone infusion of 500 mg was administered intravenously for three days, and then methylprednisolone was continued orally at 32 mg/day. Clemastine and acetylcysteine were administered to support treatment. The patient's condition improved rapidly, with normalisation of hepatic and haematological parameters, subsidence of the nodular reaction and gradual subsidence of skin lesions within two weeks.

NEUTROPENIC FEVER

A female patient, aged 58, with psoriatic arthritis (PsA), treated with sulphasalazine at 2 g/day with folic acid supplementation. No history of other chronic conditions. After 16 days of treatment, a fever of over 39°C and itchy, painful erythema all over the body. The patient reported to A&E, and her full blood count revealed leucopenia with neutropenia (WBC = 2300/L, neutrophils = 613/L) with

Table 1. DRESS diagnosis criteria according to the RegiSCAR group [3], including the scores of the patient described

	Criteria scoring			Patient score
Criteria	**NO**	**YES**	**No data**	**Patient**
Fever ≥ 38.5 °C	–1	0	–1	0
Lymphadenopathy (≥ 2 sites, > 1cm)	0	1	0	1
Atypical lymphocytes	0	1	0	0
Eosinophilia 700–1499 or 10–19.9%	0	1	0	0
≥ 1500 or 20% (with WBC <4000)		2		
Skin lesions: > 50% involvement	0	1	0	1
Rash suggestive of DRESS	–1	1	0	1
Skin biopsy — suggestive of DRESS	–1	0	0	0
Internal organ involvement (liver, kidneys, lungs, muscles or heart, pancreas, other internal organs)	0	1	0	1
- one - two or more		2		
Illness duration > 15 days	–1	0	–1	0
Exclusion of other potential causes: blood culture, ANA, serological tests (HAV, HCV, EBV, CMV, chlamydia, mycoplasma) if test results are negative and ≥ 3 of the above criteria are not met	0	1	0	1
				Total 5

Final score < 2 — DRESS ruled out; 2–3 — possible DRESS; 4–5 — probable DRESS; > 5 — definite DRESS

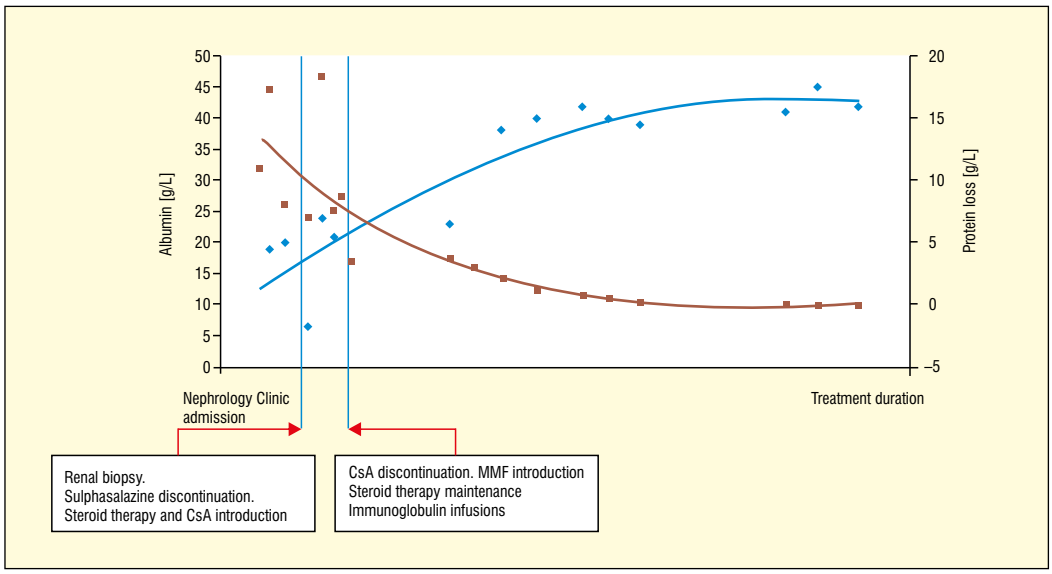

Figure 1. Severe nephrotic syndrome during sulphasalazine therapy. Monitoring of treatment effectiveness based on serum albumin and proteinuria levels

no other abnormalities. Sulphasalazine therapy was discontinued, and paracetamol, an antihistamine drug, was administered. The fever subsided within two days, and the skin lesions cleared up completely after about two weeks. In a follow-up examination after one month, WBC = 4400/L, Ne = 1400/L. Methotrexate was included in the modifying treatment of PsA with good tolerance.

SEVERE NEPHROTIC SYNDROME

A female patient, aged 47, with rheumatoid arthritis (RA), treated with sulphasalazine 2 g/day with folic acid supplementation since diagnosis. No other co-morbidities. Initially, treatment effectiveness and tolerance were good. Approximately 1.5 years after starting sulphasalazine therapy, fatigue and oedema of the lower extremities appeared, with symptoms increasing slowly. The patient attributed them to menopause and the hot weather during the summer. After about two months, ascites additionally developed; only then did the patient consult her GP. General urinalysis revealed 29 g/L protein. The patient was urgently admitted to the Nephrology Clinic. During hospitalisation, massive non-selective proteinuria (17.4 g/L), hypoalbuminaemia (17 g/L) with symptoms of hypovolaemic shock, hypocalcaemia (1.89 mmol/L), hypercholesterolaemia (total cholesterol = 17 mmol/L; LDL = 13 mmol/L) and blood clotting disorders were observed. The labelled ANA showed the presence of antinuclear antibodies in a titre of 1:1280 with a homogeneous, granular luminescence pattern. An immunoblot showed the presence of antihistone antibodies. The renal biopsy showed an early stage of focal segmental glomerulosclerosis. Methylprednisolone (32 mg/day) and cyclosporine (CsA) (150 mg/day) were introduced to treatment. Until the renal biopsy, the patient continuously received sulphasalazine; only after the histopathology result was therapy with this drug stopped. Approximately two weeks later, the patient was hospitalised again due to the deterioration of her condition, with symptoms of thrombosis of the left popliteal vein and an abscess in the subcutaneous tissue of the left thigh. Increased severity of nephrotic syndrome symptoms (proteinuria up to 20 g/L, hypoalbuminaemia = 6.5 g/L) was observed. Seven cycles of plasmapheresis were performed. The patient required multiple albumin transfusions. Immunosuppressive treatment was modified: CsA was discontinued, mycophenolate mofetil (MMF) was added to the therapy at 2 g/day, and steroid therapy was maintained. She received multiple immunoglobulin infusions for a year due to secondary hypogammaglobulinaemia. The steroid dose was then gradually reduced until it was discontinued approximately 14 months after admission to the Nephrology Clinic, and MMF was reduced to 500 mg/day. Eventually, complete proteinuria subsidence was observed approx. 16 months after the start of nephrology treatment (Fig. 1).

Table 2. Adverse reactions during sulphasalazine treatment (based on [1, 6])

	Adverse reactions during sulphasalazine treatment
Common (> 1/100 patients)	Headache, fever, decreased appetite, leucopenia, haemolytic anaemia, macrocytosis, abdominal pain, nausea, gastrointestinal disorders, increased liver enzymes, rash, pruritus, erythema, transient oligospermia, induction of autoantibodies.
Uncommon (< 1/100)	Dizziness, agranulocytosis, thrombocytopenia, depression, tinnitus.
Rare	Facial oedema, pancreatitis, pseudomembranous colitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, hepatitis, dyspnoea, cough, arthralgia and myalgia, peripheral neuropathy, encephalopathy, aseptic meningitis, nephrotic syndrome, proteinuria, haematuria, interstitial nephritis, pericarditis, systemic lupus erythematosus, serum sickness.

Note: adverse reactions occur more frequently and are more severe in patients who are so-called "slow acetylators"

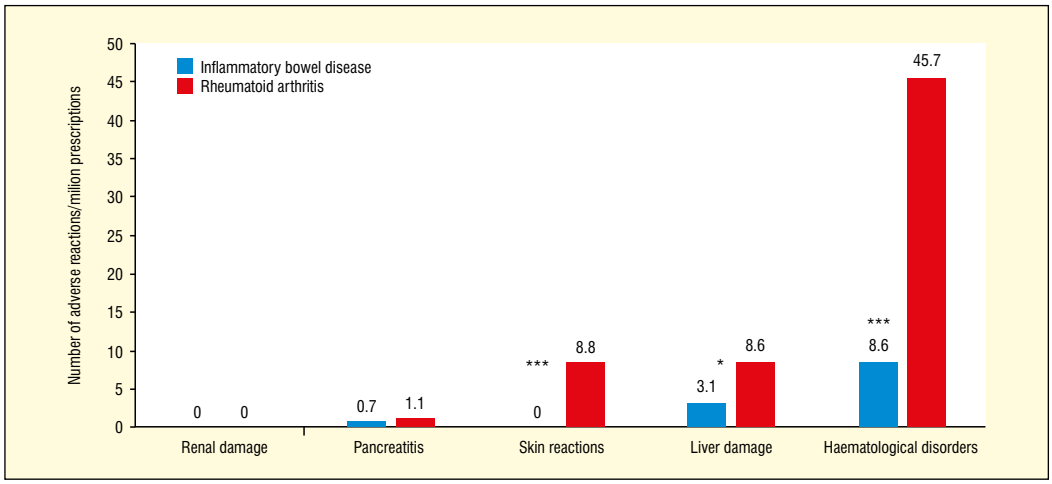

Figure 2. Estimated number of adverse reactions to sulphasalazine per million prescriptions according to the condition for which it was prescribed between 1991 and 1998 (χ^2 test: *p < 0.01, ***p < 0.001). Only patients diagnosed with inflammatory bowel disease or rheumatoid arthritis were included (based on [4])

DISCUSSION

Sulphasalazine causes mild adverse reactions (dyspeptic disorders, increased liver enzymes, decreased appetite, mild leucopenia) in approximately 25–50% of patients. Severe life-threatening adverse reactions are rare, among which haematological disorders (71%), liver damage (14%), severe skin reactions (11%), renal damage (3%) and pancreatitis (1%) are the most common (Tab. 2).

These severe adverse reactions, particularly haematological disorders, have been reported more frequently in patients taking sulphasalazine for RA than inflammatory bowel disease (IBD) [4, 5] (Fig. 2).

Approximately 20–30% of RA patients treated with sulphasalazine discontinue therapy due to adverse reactions to the drug [6]. Among the likely risk factors for sulphasalazine hypersensitivity is impaired detoxification leading to accumulation of its metabolite, i.e. sulphapyridine, in the blood, especially in patients with slower liver metabolism. In European countries, including Poland, approx. 60% of the population has the phenotype responsible for the slow progression of this process. These are the so-called "slow acetylators". Other possible causes of drug hypersensitivity include the involvement of human herpesvirus 6 (HHV-6) reactivation and genetic predisposition [7]. The diagnosis of most allergic reactions to drugs, including sulphasalazine, is based on typical history, physical symptoms and non-specific laboratory findings without definitive confirmation by drug-specific tests. The exact immunopathogenetic mechanism of the drug-induced hypersensitivity reaction cannot always be established. The clinical picture often indicates a mixed mechanism of allergic reaction. Taking into account the division by Gell and Coombs, the most common reactions are type IV (delayed reaction mediated by cellular response) and type III (reaction mediated by immune complexes).

The cases presented here represent three of the many possible complications associated with the use of sulphasalazine. In the first patient diagnosed with DRESS syndrome, the atypical symptoms were initially suggestive of multiple inflammatory diseases, requiring an extensive differential diagnosis.

Relatively low ferritin levels and skin lesions other than the ‚salmon-coloured rash' ran counter to Still's disease. An infectious cause of the described lesions was also ruled out.

A hypersensitivity reaction to sulphasalazine was indicated by the temporal relationship between the initiation of therapy with this drug and the onset of symptoms, a generalised, confluent micropapular rash and a reported history of rash following previous use of Biseptol (a combination of sulphamethoxazole and trimethoprim). DRESS syndrome is a severe, potentially life-threatening drug reaction presenting with fever, skin lesions and signs of internal organ failure. DRESS syndrome is most commonly caused by antiepileptic drugs, sulphonamides (incidence 1:10 000), allopurinol and gold salts.

It is a type IV b delayed drug hypersensitivity reaction. The DRESS mortality rate is estimated to be approx. 10% and depends on the involvement of internal organs. Liver failure is the most common cause of death in this syndrome [7, 8]. Knowledge of the clinical picture and the most common drugs that can lead to the development of DRESS syndrome contributes to a quicker diagnosis and implementation of appropriate management, reducing the risk of lethal outcomes.

In the second patient with neutropenic fever, the development of further life-threatening complications was probably prevented thanks to the rapid identification of sulphasalazine as the causative agent and the withholding of its administration. However, the risk of leucopenia during sulphasalazine treatment is highest during the first three months. Awareness of the risk of such a complication dictates that these patients should be monitored more closely, especially during the first months of sulphasalazine use [4].

Between the introduction of sulphasalazine and the onset of symptoms of nephrotic syndrome, the last patient remained under constant rheumatological supervision. Visits took place every 3 months and then every 6 months. Transaminase activity and full blood count with blood smear were systematically monitored during this time. Only once during the initial treatment stage was a creatinine determination and general urinalysis performed, which were normal at the time.

At the time of the diagnosis of nephrotic syndrome, the patient was taking only sulphasalazine and folic acid. The lesions in the renal biopsy were subtle, and the picture was not entirely consistent with the clinical condition at the time. Antinuclear antibodies typical of drug-induced lupus erythematosus (DILE) and systemic lupus erythematosus (SLE) were observed in the antinuclear antibody test [9]. Therefore, the analysis of the causes of renal damage primarily considered the involvement of immune mechanisms and the adverse reactions to sulphasalazine [10]. The patient did not meet the criteria for lupus nephritis under the 2019 ACR. The histologically described focal segmental glomerulosclerosis (FSGS) is a group of nephropathies induced by toxins, drugs or viral infections, and therefore sulphasalazine was considered the causative agent. Renal damage is one of the very rare complications of sulphasalazine therapy. Its most common manifestation is nephrotic syndrome, as observed in the case described.

CONCLUSIONS

Hypersensitivity to sulphasalazine presents a wide variety of clinical pictures, making it difficult to establish the diagnosis quickly. Some potential complications, such as DRESS syndrome, neutropenic fever or nephrotic syndrome, which we describe, can pose a direct threat to the patient's life. Detailed medical history and rapid differential diagnosis are essential in diagnosing sulphasalazine-related complications. Unfortunately, there are no commonly available laboratory tests that can confirm a hypersensitivity reaction.

The cornerstone of treatment is to discontinue the drug causing the reaction. Prompt implementation of appropriate management improves prognosis and reduces the risk of severe, life-threatening complications.

Most, i.e. approximately 76%, sulphasalazine-related adverse reactions occur within three months of starting therapy, so safety monitoring of sulphasalazine therapy should be most intense during this period [11].

Before starting sulphasalazine treatment and every two weeks during the first three months of its use, full blood count, including blood smear, and liver function should be monitored. These examinations should be carried

out every fourth week for the next three months and every third month after that. Before and during treatment, renal function parameters: creatinine levels and general urinalysis should be monitored regularly. Patients taking sulphasalazine should be advised to seek immediate medical attention if they develop fever, sore throat, malaise or other non-specific complaints, especially during the first months of treatment. The patient should also be instructed to avoid taking medicines that have caused allergic reactions and that show cross-reactivity.

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