High toxicity of sulfasalazine in adult-onset Still’s disease


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Abstract

Objective
Sulfasalazine (SSZ) is an anti-rheumatic drug that has been used to treat chronic arthritis. In many reports, the use of SSZ in children with systemic onset juvenile rheumatoid arthritis (JRA) revealed frequent side effects which required discontinuation of the drug. We examined whether there were frequent side effects of SSZ in patients with adult-onset Still’s Disease (AOSD).

Methods
From July 1990 to April 1998, we followed 41 AOSD patients. Ten were given SSZ for the treatment of arthritis and the side effects were studied. We also studied 109 consecutive patients with RA who had been given SSZ, as a control group. In addition, we retrospectively studied the side effects and efficacy of SSZ in both groups through their medical records.

Results
Six patients (60%, p < 0.01) with AOSD experienced side effects ranging from mild ones like abdominal pain, nausea and vomiting, urticaria, and facial flushing to severe ones such as high fever, hypotension, and severe myelosuppression as well as fulminant hepatitis, which led to the death of one patient. However, 16 patients (14.7%) with RA stopped using SSZ due to mild side effects such as rash, arthralgia, gastrointestinal troubles, mild leukopenia, and fever. Three AOSD patients (30%, p = 0.053) and 15 RA patients (13.8%) stopped using SSZ due to its inefficacy.

Conclusion
We conclude that SSZ appears to have frequent severe side effects in AOSD, as in systemic onset JRA. These potential adverse effects of SSZ should be considered when it is used to treat chronic arthritis with systemic symptoms. Further study of SSZ in the treatment of AOSD in a multi-center, placebo-controlled environment is needed.

Introduction
Adult-onset Still’s disease (AOSD), an adult variant of systemic onset juvenile rheumatoid arthritis (JRA), is a rare systemic inflammatory disease entity and the diagnosis is solely clinical and often difficult because clinical and laboratory features are not pathognomonic. The major features of the disease are a high spiking fever, a typical rash, polyarthritis and neutrophil leukocytosis (1, 2). Other minor findings are sore throat, lymphadenopathy or splenomegaly, liver dysfunction, negative rheumatoid factor (RF) and antinuclear antibody (ANA). The etiopathogenesis is unknown and its treatment is still not established. Approximately 25% of all patients respond to non-steroidal anti-inflammatory drugs (NSAID) alone such as enteric-coated aspirin and indomethacin. Generally, prednisolone is needed initially to control the systemic and joint manifestations and to achieve remission. Alternative therapies including disease-modifying anti-rheumatic drugs (DMARDs) such as intramuscular gold, hydroxychloroquine (HCQ), sulfasalazine (SSZ), penicillamine and, recently, immunosuppressive agents have been used to control chronic arthritis and chronic systemic diseases (3). However, these agents are not always useful because high doses or long-term treatments sometimes induce drug toxicity. Many reports have pointed out that the use of SSZ in children with systemic onset JRA can produce side effects that require discontinuation of the drug (4, 5). There have been no controlled studies of the efficacy and safety of SSZ in AOSD in addition to other DMARDs. In this study, we wish to report our experience regarding the side effects of SSZ in patients with AOSD.

Materials and methods
In this study, 41 patients with AOSD who attended our hospital from July 1990 to April 1998 were identified. All patients matched the preliminary criteria for the classification proposed by Yamaguchi et al. (6). Briefly, 5 or more criteria were required for the diagnosis, including 2 or more major criteria: fever (39°C or higher), arthralgia (lasting more than 2 weeks), typical rash, and leukocytosis with granulocytosis; minor criteria include sore throat, lymphadenopathy and/or splenomegaly, liver dysfunction, and negative RF/ANA. Patients with infections, malignancies, and other rheumatic diseases were excluded. Ten of the 41 patients had been treated with SSZ (enteric-coated tablets). The profiles of their...
side effects were examined retrospectively by reviewing their medical records.

As a control group, 109 consecutive patients with rheumatoid arthritis (RA) (fulfilling the criteria of the American College of Rheumatology) who were treated with SSZ were selected and the side effects of their SSZ treatment were examined. In addition, we reviewed laboratory findings that included WBC counts, ESR, liver function, serum ferritin, RF and ANA > 1:80. Then we studied the side effects of SSZ and identified the cases in which SSZ use was stopped. Inefficacy was defined as the absence of clinical improvement in arthritis despite SSZ treatment over a 3-month period (7). A Fisher’s exact test was used to compare the proportions of side effects and discontinuation of SSZ usage in both groups.

Results

A total of 41 patients with AOSD were enrolled and their charts were reviewed. Their mean age was 31.9 years (range 16-57 years) and the mean duration of the disease was 3.5 years (range 1-14 years). Their clinical and biological characteristics are listed in Table I. As expected, a preponderance of females (32 patients, 78%) was observed in the study. The most common presenting symptoms of AOSD were fever (97.6%), arthritis (92.7%), and transient rash (75.6%). Positive ANA occurred in 7.3% of the patients. Among the AOSD patients, 10 were given SSZ for the control of arthritis and 6 (60%) experienced side effects (Table II). Most of remaining patients were treated with prednisolone, NSAID, or one or two DMARDs including HCQ, methotrexate (MTX), oral gold, and azathipurine.

The duration of SSZ treatment before the appearance of side effects varied from 10 days to 94 weeks. The average dosage of SSZ was 1.3 gm which was not high for most patients. As can be seen in Table III, adverse effects related to SSZ in AOSD were not only mild symptoms such as abdominal pain, nausea and vomiting and facial flushing (pts. A and B), but also significant symptoms such as high fever in 3 patients (pts. B, C, D), hypotension in 1 patient (pt. B), and severe myelosuppression in 1 patient (pt. E). Another patient (pt. F) died of fulminant hepatitis with azotemia after 2 weeks of receiving SSZ 1.0 gm per day. Five patients experienced side effects of SSZ during the first 5 weeks of therapy. Patient B experienced side effects with SSZ 3 times. Patient E experienced pan-cytopenia after use of SSZ 1.0 gm/day for 2 weeks. His WBC counts suddenly dropped to 500/mm$^3$ from 20,000/mm$^3$ but returned to normal values with granulocyte-colony stimulating factor (G-CSF) after stopping SSZ. Patient F developed fulminant hepatic failure with acute renal failure after using SSZ for 12 days and died after 2 days of hospitalization.

In contrast, 16 patients out of 109 with RA stopped SSZ therapy due to mild side effects such as rash, urticaria, gastrointestinal troubles, mild leukopenia, and fever which were relatively reversible. Therefore, when we compared the incidence of side effects of SSZ, they were significantly more frequent in the AOSD patients (60%) than in the RA group (14.7%).

With respect to the discontinuation rate due to inefficacy, 3 patients with AOSD (30%) and 15 patients with RA (13.8%) stopped due to inefficacy. One patient with AOSD who had used SSZ had been treated in combination with MTX and HCQ without any specific adverse effects. More data is needed to show the statistical significance.

Discussion

Many drugs have been used to improve
the clinical outcome in AOSD, including various NSAIDs, DMARDs (anti-malarials, penicillamine, gold), and immunosuppressive drugs such as MTX (8, 9), cyclophosphamide, and azathioprine. Also, anecdotal reports suggest that these drugs may be beneficial. However, the response to treatment is difficult to evaluate because of the remittent nature of the disease, the different drug dosages used, and uncontrolled clinical settings. SSZ has been successfully used to treat RA (10) and the seronegative spondyloarthropathies. In addition, SSZ has shown encouraging results in an open trial on JRA patients (11). However, up to 50% of patients develop a variety of side effects within the first 4 months of treatment, the majority being mild and reversible. Side effects include skin rash, nausea and abdominal pain, hepatic enzyme abnormalities, central nervous system disturbances, and blood dyscrasias.

Instances of liver toxicity induced by SSZ have been noted in adult RA and JRA patients. Farr and co-workers reported 2 RA patients with reversible hepatic dysfunction and an overall 2.5% rate of liver toxicity in 200 adult patients with RA who received SSZ (12). They also reported that 58% of 200 patients with inflammatory joint diseases developed one or more adverse reactions and in 21.5% the drug was withdrawn, although in only 5% were the side effects judged to be potentially dangerous (13). Many studies of the use of SSZ in children with Still’s disease reported side effects requiring the interruption of treatment (11, 14). Caspi et al. reported the first case of liver toxicity induced by SSZ in Still’s disease (15). Many authors even consider SSZ to be contraindicated in Still’s disease, particularly if the disease is systemically active (16).

In our study, the use of SSZ in AOSD also revealed frequent severe side effects that required stopping the drug. The average duration of the published SSZ trials was 38.6 weeks, but most of the side effects in this present study occurred within 5 weeks except one. Besides side effects such as gastrointestinal symptoms, 3 of 6 patients with AOSD experienced high fever after the SSZ trial. One patient developed fulminant toxic hepatitis within 12 days after SSZ 1 gm and this might be associated with SSZ hyper-sensitivity.

Lever abnormalities, in the form of both hepatomegaly and elevation of hepatic enzyme, and disseminated intravascular coagulopathy have been reported in AOSD (17). This may be induced by NSAIDs as well as DMARDs and seems to occur especially during the active phase. To the best of our knowledge, there are few reports of the side effects of SSZ except for one case of SSZ-induced hepatitis in AOSD (18). The authors suggested that sulfapyridine could also undergo hydroxylation mediated by cytochrome P450, although the acetylator status was a major determinant of the pharmacokinetics. Therefore, the interleukin-1 released in AOSD might be capable of reducing hepatic cytochrome P450 and such a mechanism could account for an alteration in drug metabolism and the increase potential for adverse reactions.

We would like to emphasize the high toxicity of SSZ in AOSD from our results. However other drugs, notoriously NSAIDs and other DMARDs, may also give rise to adverse effects. Although our data were obtained from a relatively limited group, we conclude that when using SSZ to control arthritis in AOSD, the potential adverse effects of SSZ should be carefully considered. Multi-center, placebo-controlled studies should be done in the future.

### References