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ORIGINAL ARTICLE

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Gastrointestinal symptoms associated with enteric-coated sulfasalazine (Azulfidine EN tablets)

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Abstract To investigate both the incidence and the dosage used to treat gastrointestinal (GI) symptoms associated with enteric-coated sulfasalazine (Azulfidine EN, AZL) in patients with rheumatoid arthritis (RA), we studied the clinical history of 153 RA patients, and any available data on GI symptoms that might have been associated with AZL. GI symptoms appeared in 64 (42.5%) of the 153 cases. There were 19 events of nausea, vomiting, or dyspepsia, 14 events each of epigastric discomfort and reduction or loss of appetite, 10 events of epigastric, stomach, or abdominal pain, 9 events of heartburn, 8 events of mouth ulcer, 3 events each of loss of taste and abdominal bloating or borborygmus, 2 events each of diarrhea or loose stools, hematemesis or melanemia, and gastric or esophageal ulcer, and 1 event of stomatitis. These results indicate that GI symptoms associated with AZL are usually mild and treatment can continue, with almost all cases responding to a reduction in dose or drug cessation. In some cases, a histamine receptor-2 blocker or proton pump inhibitor is also required.

Key words Adverse drug reactions (ADRs) · Azulfidine EN (AZL) · Disease-modifying antirheumatic drugs (DMARDs) · Gastrointestinal (GI) symptoms · Rheumatoid arthritis (RA) · Sulfasalazine (SSZ)

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Introduction

Sulfasalazine (SSZ) was developed by Svartz in Sweden in the 1940s as an antirheumatic drug,[1,2] but because it was not an enteric-coated tablet, gastrointestinal (GI) disorders were common. Enteric-coated SSZ tablets (Azulfidine EN, AZL) were developed in the 1970s to reduce these GI symptoms, and the drug's usefulness against rheumatoid arthritis (RA) was demonstrated in Europe.[3] Since then, AZL has been used in about 50 countries worldwide as a disease-modifying antirheumatic drug (DMARD), and was released in Japan in 1995.

The onset of action of AZL is relatively rapid compared with other DMARDs, and because there is a relative lack of serious adverse drug reactions (ADRs), it is commonly used in early RA. Nonetheless, an overall rate of ADRs of about 30%, which is similar to that for other DMARDs, has been reported. We investigated the incidence of GI symptoms associated with AZL in RA patients visiting our hospital, as well as measures used to treat these symptoms.

Materials and methods

Data were collected on the background of RA patients visiting our hospital who had been prescribed AZL, and on any suspect GI symptoms, e.g., type, date of onset, and any treatments used. There were 153 cases (32 men, 121 women) with an average age of 60.2 years (range 32–89 years). By the radiographic stage, there were 24 cases in stage I, 19 in stage II, 30 in stage III, 26 in stage IV, and 54 whose stage was unkown. By functional class, there were 5 cases in class I, 71 in class II, 19 in class III, none in class IV, and 58 whose class was unknown. Of the 153 cases, 72 had experienced ADRs from DMARDs, 71 had not experienced any ADRs, and 10 did not know. The dosage of AZL was not more than 1 g/day in all cases, and the mean treatment duration was 332 days (range 1–1705 days).

An evaluation of the efficacy of AZL was performed by the treating physician, taking into account the patient's im-

Table 1. Gastrointestinal (GI) symptoms

	Occurrences	%
Nausea, vomiting, or dyspepsia	19	(12.4)
Epigastric discomfort	14	(9.2)
Reduction or loss of appetite	14	(9.2)
Epigastric, stomach, or abdominal pain	10	(6.5)
Heartburn	9	(5.9)
Mouth ulcer	8	(5.2)
Loss of taste	3	(2.0)
Abdominal bloating or borborygmus	3	(2.0)
Diarrhea or loose stools	2	(1.3)
Hematemesis or melanemia	2	(1.3)
Gastric or esophageal ulcer	2	(1.3)
Stomatitis	1	(0.7)
Total	87	

pressions and the results of investigations, and the efficacy was rated as effective, ineffective (primary ineffectiveness), or loss of efficacy (secondary ineffectiveness). Cases who had been taking AZL for less than 1 month, because of ADRs or for other reasons, were not assessed.

Results

Incidence and types of gastrointestinal symptoms

A total of 87 instances of GI symptoms were reported in 64 (41.8%) of the 153 cases (Table 1). GI symptoms only occurred in 47 cases (73.4%), and ARDs in addition to GI symptoms occurred in 17 cases (26.6%). These other ADRs were 11 occurrences each of fever or rash, 7 occurrences of hematological disorder, 2 occurrences of hepatic disorders, and 1 occurrence of edema.

Time of onset of gastrointestinal symptoms

The total number of occurrences, with time of onset of GI symptoms, and the total number of cases where treatment was stopped were 10 and 4 within 1 week, 16 and 7 within 2 weeks, 30 and 14 within 1 month, and 50 and 19 within 3 months, respectively. The numbers within 1 year were 69 and 26, respectively, and within 2 years were 82 and 30, respectively (Table 2).

Patient's background factors in cases of gastrointestinal symptoms

No correlations were found between the patient's background factors, history of ADRs from any DMARDs, stage, class, dose of AZL, or concomitant drugs (non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, DMARDs). There was a tendency toward a higher incidence of GI symptoms in the group taking 0.5 g/day of AZL drug than in the group taking 1 g/day (epigastric, stomach, or abdominal pain, 14.0% and 4.8%; mouth ulcer, 10.3% and 4.0%). However, this difference was not significant. There was a significant difference only in whether or not the patient took glucocorticoid: reduction or loss of appetite was 21.4% and 6.4%, respectively ($P < 0.05$), and epigastric, stomach, or abdominal pain was 25.0% and 2.4%, respectively ($P < 0.01$).

GI symptoms occurred regardless of whether patients were also taking NSAIDs. However, nausea, vomiting, or dyspepsia (18.8%) and reduction or loss of appetite (12.5%) occured more frequently with more selective cyclooxygenase-2 (COX-2) inhibitors such as diclofenac or etodolac.

Treatment of gastrointestinal symptoms

Of the 87 instances of GI symptoms, the dose of AZL was continued or reduced in 47 cases, no treatment was given in 31 cases, and 16 cases were given antacids/digestive aids. Of the 40 occurrances in which AZL treatment was suspended or discontinued, no treatment was given in 32 cases, and 8 were given antacids/digestive aids. The symptoms resolved in all cases (Table 3). The one case of stomatitis had not resolved at a follow-up 1 year after AZL was stopped.

Clinical efficacy

AZL was rated as efficacious in 88 cases (80%), as exhibiting loss of efficacy in 10 cases (9.1%), and as ineffective in 12 cases (10.9%). The drug was not evaluated in 43 cases because the treatment had lasted for less than 1 month (Table 4). Including the cases of loss of efficacy, there was no significant difference between patients with GI symptoms (92.5%) and those without (87.1%).

Discussion

We investigated the incidence of GI symptoms associated with AZL in RA patients visiting our hospital. We had intended to perform a comparative study between AZL and Salazopyrin (plain tablets of SSZ), but were only able to perform a noncomparative retrospective study because the only indication for Salazopyrine in Japan is ulcerative colitis (UC), and Abramson et al.[4] and Weaver et al.[5] had already shown that the incidence of GI symptoms with AZL was lower than that with Salazopyrine in RA and UC patients.

Because RA is a systemic disease, some GI symptoms may arise from the disease process itself, although they are nonspecific.[6] When GI symptoms arise, they are usually because of complications such as amyloidosis, or due to treatment with NSAIDs or DMARDs.

The most common ADR of AZL is GI symptoms. Nishioka et al.[7] reported an ADRs frequency of 21.9%, of which 11.5% were GI symptoms. We found a high incidence of GI symptoms (41.8%), but we included some very mild symptoms that would normally be overlooked. ADRs to AZL typically occur early, with 73.5% occurring within 1

Table 2. Time of onset of gastrointestinal (GI) symptoms

	≤1 w	≤2 w	≤1 m	≤2 m	≤3 m	≤4 m	≤5 m	≤6 m	≤7 m	≤8 m	≤9 m	≤10 m	≤11 m	≤12 m	≤24 m	24 m<	Total
Nausea, vomiting, or dyspepsia	4	2	3		2			1		1	1	1			3	1	19
Epigastric discomfort	2		3	2	1	1		1		1			1		2		14
Reduction or loss of appetite	2	2	2						1			1	1		4	1	14
Epigastric, stomach, or adominal pain	1	2			2		1		1	1					1	1	10
Heartburn	1		1	2	2			1							1	1	9
Mouth ulcer			2	3	1							1			1		8
Loss of taste			1	1											1		3
Abdominal bloating or borborygmus			1				1									1	3
Diarrhea or loose stools					1		1										2
Hematemesis or melanemia				1						1							2
Gastric or esophageal ulcer				2													2
Stomatitis			1														1
Total occurrences (Total discontinued cases)	10 (4)	6 (3)	14 (7)	11 (3)	9 (2)	1 (1)	3 (2)	3 (1)	2	4	1	3 (1)	2 (2)	0	13 (4)	5 (2)	87 (32)
Cumulative total (Total cumulative discontinued cases)	10 (4)	16 (7)	30 (14)	41 (17)	50 (19)	51 (20)	54 (22)	57 (23)	59 (23)	63 (23)	64 (23)	67 (24)	69 (26)	69 (26)	82 (30)	87 (32)	

w, week; m, month

Table 3. Treatment of gastrointestinal (GI) symptoms

	Continuation/reduction					Suspension/cessation				
	Nontreatment	H2B[a]	PPI[b]	Other digestive	Total occurrences	Nontreatment	H2B[a]	PPI[b]	Other digestive	Total occurrences
Nausea, vomiting, or dyspepsia	7	1	1	2	11	4		2	2	8
Epigastric discomfort	5		1		6	7			1	8
Reduction or loss of appetite	4	1		1	6	8				8
Epigastric, stomach, or abdominal pain	5		1	1	7	3				3
Heartburn	4		1	2	7	2				2
Mouth ulcer	1			1	2	3			3	6
Loss of taste	1		1		2	1				1
Abdominal bloating or borborygmus	1				1	2				2
Diarrhea or loose stools	1				1	1				1
Hematemesis or melanemia	2				2					0
Gastric or esophageal ulcer			1		1	1				1
Stomatitis				1	1					0
Total occurences	31	2	6	8	47	32	0	2	6	40

[a] Histamine receptor-2 blocker
[b] Proton pump inhibitor

Table 4. Clinical efficacy

	Without GI symptoms	With GI symptoms	Total cases
Effectiveness	53	35	88
Loss of efficacy	8	2	10
Ineffectiveness	9	3	12
Total cases	70	40	110

43 cases were not assessed

month,[7] and 71%[8] or 76%[9] within 3 months. We found 50 instances of GI symptoms within 3 months, by which time the treatment had been discontinued in 19 cases (29.7%). However, some GI symptoms did develop after 3 months, and these included a case of melanemia after 8 months. Eighteen cases had discontinued treatment after 1 year.

The patient's background factors, such as age, history of ADRs from any DMARDs, and history of GI ulcer, can affect the development of GI symptoms, but these trends were not found in our study. This may reflect the fact that we routinely prescribe antiulcer medication to patients with a history of GI ulcer.

Regarding concomitant medication, low doses of oral glucocorticoid (2.5–5.0 mg/day) have been reported to decrease the incidence of all ADRs significantly,[8] but we found that the concomitant use of glucocorticoid significantly increased the incidence of reduction or loss of appetite, and of epigastric, stomach, or abdominal pain. On the other hand, the comcomitant use of NSAIDs had no effect, and because the GI symptoms were still observed with selective COX-2 inhibitors, we concluded that these GI symptoms were indeed due to AZL.

The usual dose of AZL for RA outside Japan is 2–3 g/day. Skosey[10] reported that most patients with GI symptoms have their problem alleviated by a reduction in dosage to 1 g/day, and Nishioka et al.[7] reported that in Japan the incidence of ADRs with 1 g/day was less than that with 2 g/day. In the present study, however, no difference in the incidence of GI symptoms was seen between daily dosages of 0.5 and 1.0 g. Indeed, some symptoms were more common at the lower dosage, showing little correlation between dose and the incidence of GI symptoms at doses less than 1.0 g/day.

GI symptoms improved in 72.4% of cases with continuation/reduction or suspension/cessation of AZL. The decision whether to continue or discontinue the administration of the offending medication in the case of GI symptoms depends largely on the receptivity of the patient. In the present study, 27.6% of cases improved rapidly with antacids/digestive aids such as histamine receptor-2 blockers (H2B) or proton pump inhibitors (PPI). In cases of hematemesis or melanemia, however, AZL should be discontinued and the patient managed appropriately.

The etiological mechanisms of GI symptoms related to AZL are unclear. Some form of allergy may be involved, because these symptoms appear soon after the start of treatment, a dose–response relationship is not observed at the 0.5 and 1 g/day dosages, allergic symptoms such as fever or rash are seen, there have been some cases of shock,[11] and the incidence of GI symptoms is reduced when glucocorticoids are taken concomitantly.[8] On the other hand, the fact that hypersensitivity and GI symptoms are increased at dosages greater than 2 g/day[9] could indicate a dose–response pattern and a mechanism involving prostaglandins, as is the case with NSAIDs. The types of GI symptoms have not altered in the change from an uncoated to an enteric-coated tablet, but the incidence of such symptoms has decreased by about 40%,[4] so a direct effect on the GI mucosa may be involved. However, caution is needed in deciding whether to attribute stomatitis to AZL, because it can also be caused by mechanical irritation, reduced saliva production, such as in Sjögren's syndrome, and by viral infections and other conditions.

Our results indicate that GI symptoms associated with AZL are usually mild and that treatment can continue, with all cases responding to a reduction in dose or cessation of AZL, and in some cases the addition of a H2B or PPI.

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