



Early View

Research letter

Two cases of nintedanib-induced diarrhoea treated using a 5-HT type 3 receptor antagonist

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Two cases of nintedanib-induced diarrhoea treated using a 5-HT type 3 receptor antagonist

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Take Home Message

Nintedanib-induced diarrhoea may be controlled by ramosetron by modulation of intestinal motility as for irritable bowel syndrome

To the Editor:

Nintedanib has been used in the management of patients with idiopathic pulmonary fibrosis (IPF) and progressive pulmonary fibrosis (PPF) [1, 2]. The

most common adverse event associated with nintedanib is diarrhoea. In the INPULSIS and INBUILD trials, more than 60% of patients reported diarrhoea [1, 2]. Anti-diarrhoeal medications, including loperamide, are usually administered and are adequate in some patients. However, a significant proportion of patients continue to experience frequent diarrhoea, even after anti-diarrhoeal treatment. In the INBUILD trial, approximately 30% of patients, who experienced diarrhoea at least once, required dose reduction or discontinuation of nintedanib [2]. Hence, new treatments for diarrhoea are needed to improve quality of life in these patients. Ramosetron, a serotonin (5-hydroxytryptamine) type 3 (5-HT₃) receptor inhibitor used for diarrhoea-predominant irritable bowel syndrome (IBS), might be a suitable treatment for nintedanib-induced diarrhoea [3] and has a low risk of hard stool (1.11%) and constipation (1.11%) [4].

We have treated two patients with nintedanib-induced diarrhoea using ramosetron (Irribow®; Astellas Pharma, Tokyo, Japan). One patient had IPF (case 1) and the other had sarcoidosis complicated by autoimmune pulmonary alveolar proteinosis with PPF (case 2); the first case fulfilled the updated criteria for IPF and the second fulfilled those for PPF [5]. Both patients continued to experience severe diarrhoea despite starting loperamide. In case 1, inflammatory bowel disease and cancer were ruled out by colonoscopy. Both cases 1 and 2 experienced severe diarrhoea while under observation for more than one year after the start of nintedanib. Their treating gastroenterologist and psychotherapist considered that their symptoms were similar to diarrhoea-predominant IBS (IBS-D) and recommended administration of

ramosetron. We prescribed ramosetron in both cases and noticed improvement of diarrhoea within the first 3 days. Case 1 stopped daily use of loperamide within 10 days and case 2 stopped using it completely from the next day onwards. The long-term effects of ramosetron were monitored by patient interviews, medication history-taking, and assessment of the severity of diarrhoea based on the Common Terminology Criteria for Adverse Events (CTCAE) grade [6] and the Bristol Stool Form Scale (BSFS) [3]. The BSFS delineates types 1 and 2 as constipation, types 3, 4, and 5 as normal stool, and types 6 and 7 as diarrhoea (Table 1) [3].

Diarrhoea remained improved after two months of treatment with ramosetron (Table 1). The CTCAE grade improved from 3 to 2 in case 1 and from 2 to 1 in case 2. Furthermore, the BSFS type changed from 6 or 7 in both cases to 5 in case 1 and 3 or 4 in case 2. In both cases, stool samples became normal. Case 1 continued to take loperamide about once a week and case 2 stopped it almost completely. The dose of ramosetron was reduced from 5 µg daily to 5 µg on alternate days in case 2 because the patient was completely free of diarrhoea and feared constipation. Both patients were satisfied with the efficacy of ramosetron in that they could go out without feeling anxiety about diarrhoea.

The pathophysiology of nintedanib-induced diarrhoea is unknown. Nintedanib is a tyrosine kinase inhibitor (TKI) that inhibits signal transduction via platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF) [1,2]. According to the European Society for Medical Oncology clinical practice guidelines, TKI-induced diarrhoea

is common in adult cancer patients [7]. Inhibition of the VEGF receptor by TKIs might interfere with the capillary network in the intestinal mucosa and pancreas and cause diarrhoea-like ischemic colitis through ischaemia of the intestinal mucosa and fatty diarrhoea through pancreatic ischaemia [8]. Both PDGF [9] and FGF [10] are associated with the turnover of the intestinal mucosa. TKIs that target PDGF and FGF receptors may induce diarrhoea via apoptosis of enterocytes, similar to TKIs that target the epidermal growth factor receptor. Hence, nintedanib may cause diarrhoea via these mechanisms.

An association between TKI-induced diarrhoea and 5-HT has been reported. Davies et al. reported that polymorphisms in the serotonin reuptake transporter (SERT) gene were associated with diarrhoea in patients on imatinib, a TKI that targets the PDGF receptor [11]. Bosutinib, which is a TKI similar to imatinib and inhibits 71% of SERT [11], might increase the availability of 5-HT and has the highest incidence of diarrhoea (84%) [11]. Signal transduction occurs via crosstalk between 5-HT and PDGF receptors in the tyrosine kinase pathway [12]. Therefore, 5-HT could be associated with nintedanib-induced diarrhoea in patients with IPF or PPF, although whether nintedanib inhibits SERT has not been confirmed, and ramosetron, a selective 5-HT₃ receptor antagonist, might be able to control the diarrhoea.

The primary mechanism of action of 5-HT₃ receptor antagonists in the treatment of IBS-D is thought to be slowing of intestinal transit [3]. Ondansetron, a 5-HT₃ antagonist, is known to inhibit intestinal motor activity in dogs [13]; however, alosetron, another 5-HT₃ antagonist, paradoxically activates retrograde

contraction in the left colon in patients with IBS-D [14]. Hence, further investigation is needed to determine how ramosetron as a 5-HT₃ antagonist affects intestinal motility and exerts an anti-diarrhoeal effect.

According to the European Society for Medical Oncology guidelines, loperamide can be administered at a dose of 2 mg every 2–4 hours to a maximum of 16 mg/day [8]. Ramosetron is usually administered at a dose of 5 µg/day and exhibits more prolonged 5-HT₃ receptor antagonism than other 5-HT₃ receptor antagonists [15]. The efficacy of ramosetron was confirmed within 3 days in our two cases; however, its response rate was 35.36% when administered for 1 month in IBS-D [4]. Therefore, ramosetron should be used continuously once daily, with careful administration of loperamide according to the severity of diarrhoea. Furthermore, the risk of paralytic ileus associated with these agents should be borne in mind [7].

In conclusion, nintedanib-induced diarrhoea may be controlled by ramosetron. However, the anti-diarrhoeal effects of ramosetron require confirmation in prospective trials in the future.

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Conflicts of Interest

YI is a consultant or steering/advisory committee member for Boehringer Ingelheim, Roche, SAVARA, and Taiho. YI has received lecture fees from Boehringer Ingelheim, Shionogi, Kyorin, Thermo Fisher, and GSK. TA has received lecture fees from Boehringer Ingelheim and Shionogi.

Table 1 Patient characteristics and response of nintedanib-induced diarrhoea to treatment with ramosetron

	Case 1	Case 2
Diagnosis of ILD	IPF	Sarcoidosis + APAP
Sex	Male	Female
Age at the commencement of nintedanib	68	46
Concomitant steroid therapy	No	Yes
Initial dose of nintedanib, mg/day	300	300
At the start of ramosetron		
Nintedanib dose, mg/day	200	300
CTCAE grade of diarrhoea*	3	2
Daily frequency of diarrhoea	10	4
Bristol Stool Form Scale type**	6 or 7	6 or 7
Median loperamide dose, mg/day	3	1
Subscribed loperamide, mg/month	68	24
After the start of ramosetron		
Nintedanib dose, mg/day	200	300
Ramosetron dose, µg/day	5	5
Duration of ramosetron, days [#]	239	121
Days until effects of ramosetron [§]	3	1
CTCAE grade of diarrhoea*	2	1
Daily frequency of diarrhoea	5	<1
Bristol Stool Form Scale type**	5	3 or 4
Median loperamide dose, mg/day	0	0
Days until discontinuation of loperamide [¶]	10	1
Subscribed loperamide, mg/month	0	0

*Evaluated based on CTCAE version 5.0 [6]. **Evaluated based on the guideline for irritable bowel syndrome [3]. Type 3 stool is like a sausage but with cracks on its surface. Type 4, standard stool, is like a sausage or snake, smooth, and soft. Type 5, the stool consists of soft blobs with clear-cut edges. Type 6, the stool is fluffy with ragged edges or mushy. Type 7, the stool is watery with no solid component. [#]From start of ramosetron to final dose. [§]When patients firstly noticed improvement of diarrhoea. [¶]Periodic administration of loperamide was stopped. Abbreviations: APAP, autoimmune pulmonary alveolar proteinosis; CTCAE, Common Terminology Criteria for Adverse Events; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis.

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