



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

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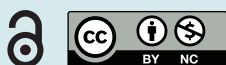
To the Editor:

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, >60% of patients reported diarrhoea [1, 2]. Antidiarrhoeal 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 antidiarrhoeal treatment. In the INBUILD trial, ~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-D), 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 >1 year after the start of nintedanib. Their treating gastroenterologist and psychotherapist considered that their symptoms were similar to 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 3–5 as normal stool, and types 6 and 7 as diarrhoea (table 1) [3].

Diarrhoea remained improved after 2 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 ischaemic colitis through ischaemia of the intestinal mucosa and fatty diarrhoea through pancreatic ischaemia [8]. Both PDGF [9] and FGF [10] are associated



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[Nintedanib-induced diarrhoea may be controlled by ramosetron by modulation of intestinal motility as for irritable bowel syndrome #pulmonaryfibrosis](https://bit.ly/3OQVAII) <https://bit.ly/3OQVAII>

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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, years	68	46
Concomitant steroid therapy	No	Yes
Initial dose of nintedanib, mg·day⁻¹	300	300
At the start of ramosetron		
Nintedanib dose, mg·day ⁻¹	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 ⁻¹	3	1
Prescribed loperamide, mg·month ⁻¹	68	24
After the start of ramosetron		
Nintedanib dose, mg·day ⁻¹	200	300
Ramosetron dose, µg·day ⁻¹	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 ⁻¹	0	0
Days until discontinuation of loperamide ^f	10	1
Prescribed loperamide, mg·month ⁻¹	0	0

ILD: interstitial lung disease; IPF: idiopathic pulmonary fibrosis; APAP: autoimmune pulmonary alveolar proteinosis; CTCAE: Common Terminology Criteria for Adverse Events. [#]: CTCAE version 5.0 [6]. [¶]: 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 first noticed improvement of diarrhoea. ^f: periodic administration of loperamide was stopped.

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.* [11] 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. Bosutinib, which is a TKI similar to imatinib and inhibits 71% of SERT, 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 antidiarrhoeal effect.

According to the European Society for Medical Oncology guidelines, loperamide can be administered at a dose of 2 mg every 2–4 h to a maximum of 16 mg·day⁻¹ [8]. Ramosetron is usually administered at a dose of 5 µg·day⁻¹ 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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