Diarrhea and the rationale to use Sandostatin®

M. Peeters[1], J. Van den Brande[1], S. Francque[2]

(1) Department of Oncology, Antwerp University Hospital ; (2) Department of Hepato-Gastroenterology, Antwerp University Hospital.

Abstract

This paper reviews the research that has been conducted into the use of Sandostatin® to control the debilitating symptoms of diarrhea in a number of different etiologies. These are cancer-related diarrheas, including diarrhea related to chemotherapy, radiotherapy, neuroendocrine tumor carcinoid syndrome, vaso-active intestinal peptide-secreting tumors and also non-cancer related diarrhea, including short bowel syndrome, ileo- and jejunostomy, dumping syndrome, graft versus host disease and AIDS-related diarrhea.

There is an increasing recognition of the need to balance the cost of care with patient outcome. It is becoming clear that although the cost of a therapeutic regimen with Sandostatin® is substantially greater than the current non-specific therapy, the overall cost is potentially greater without the use of Sandostatin® for patients with refractory diarrhea due to the inevitable need for further treatment and/or hospitalization with intravenous fluid supplementation.

Initial trials and reports from preclinical testing and clinical practice have shown promising results and, although in the majority of cases they strengthen the view taken in the published consensus guidelines for the use of Sandostatin® for refractory diarrhea, further, larger scale, comparative clinical trials are required for any evidence-based definition of dosage and efficacy as a treatment or prophylactic agent to combat and control diarrhea. (Acta gastroenterol. belg., **2010**, 73, **25-36**).

Introduction

An overall definition for diarrhea is rather difficult to formulate. If stools consistency is changing and/or the daily production of stools is more than 200 g and/or the stool frequency is exceeding 3 times a day, clinically this can be called diarrhea. Especially in older patients, the difference with fecal incontinence is sometimes difficult to make.

Based on the pathogenesis, osmotic and/or secretory diarrhea can occur. Osmotic diarrhea is related to hypertonic bowel fluid and can be induced by laxatives, diabetes or lactase deficiency. Water transportation towards the bowel lumen results in a watery diarrhea. Mostly this type of diarrhea disappears in fasting condition and by stopping laxatives. Secretory diarrhea is characterized by an imbalance between sodium/chloride resorption and chloride/sodium secretion in the small bowel. Different etiologies such as choleratoxin, VIP hormone, serotonin, can induce this type of diarrhea. In most clinical situations, such as celiac disease, the diarrhea is the sum of an osmotic and secretory fraction.

Based on the duration, acute and chronic diarrhea can be differentiated. The origin of acute diarrhea is mostly infection or medication. The maximum duration of acute diarrhea is between 2 and 3 weeks. A long list of etiologies can induce chronic diarrhea. Examples are chronic inflammatory bowel disease (ulcerative colitis and Crohn's disease), irritable bowel disease, bacterial overgrowth,… Diarrhea can also occur in many other conditions including HIV, diabetes mellitus, intestinal graft versus host disease and through the use of chemo- and radiotherapy.

Mostly treatment is challenging and etiology-based treatment of diarrhea is important. For example, antibiotics are indicated in case of bacterial infection. In an important fraction of patients, etiology-based treatment is combined with symptomatic therapy such as loperamide.

Refractory diarrhea is defined as diarrhea persisting for more than 14 days and does not respond to conventional treatments such as antimicrobial therapy or other standard, non-specific antidiarrheal medications (1,2).

For these patients there is a medical need for additional therapeutic options.

Endogenous somatostatin, produced by the hypothalamus, D-cells of the pancreas and the neuroendocrine cells throughout the GI tract, regulates endo- and exocrine secretions and inhibits the release of a number of hormones and growth factors via interaction with five somatostatin receptor subtypes ($sst_{1\text{-}5}$) (3,4). Sandostatin® (also known as octreotide, octreotide acetate and SMS 201-995), is a synthetic somatostatin analogue with high affinity for the sst_2 receptor, moderate affinity for sst_5 and weak affinity for the sst_3 receptor subtype (5-7). Sandostatin®'s interaction with these three receptor subtypes leads to an inactivation of adenylate cyclase or the inhibition of Ca^{2+} influx and K^+ efflux via inhibitory G-proteins. This action results in the inhibition of a number of pancreatic and gastrointestinal hormones, such as insulin, glucagon, thyroid-stimulating hormone, vaso-

Correspondence to : Prof. dr. Marc Peeters, Department of Oncology, Antwerp University Hospital, Wilrijkstraat 10, 2650 Edegem. E-mail : marc.peeters@uza.be

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active intestinal peptide, gastrin, secretin, motilin and insulin-like growth factor (8-12). Sandostatin® has a proven efficacy to treat conditions resulting from an overproduction of hormones including acromegaly and the symptoms of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) such as carcinoid syndrome (8,9).

In addition to the proven clinical efficacy of Sandostatin® in acromegaly and GEP-NETs, there is also a wealth of published data on the efficacy of Sandostatin® to treat diarrhea of different etiologies. The rationale for Sandostatin®'s use in refractory diarrhea is based on the drug's effects on receptors in the different locations of the gastrointestinal (GI) tract. Sandostatin® has inhibitory effects on GI motility, gastric and pancreatic endocrine secretions as well as pancreatic exocrine secretions, GI peptide release and splanchnic blood flow and stimulates the absorption of water and electrolytes (1), all of which counteract the pathogenesis and course of diarrhea. Paradoxically some of these actions of octreotide might per se cause diarrhea (loose stools) and mild steatorrhea (presumably resulting from transient inhibition of pancreatic exocrine and biliary secretion and malabsorption of fat) being a well-known side effect of therapy with octreotide. Other common adverse effects of treatment with octreotide include nausea, abdominal cramps, and flatulence. These symptoms start within hours of the first subcutanuous (SC) injection, are dose-dependent, and usually subside spontaneously within the first few weeks of treatment.

There may be local pain and erythema at the injection site. Impaired glucose tolerance or even overt diabetes mellitus have also been observed during therapy with octreotide. Long term treatment can lead to the development of gallstones and/or gallbladder sludge.

This present summary aims to provide a comprehensive review of the rationale for the use of Sandostatin® in this indication. A number of etiologies will be reviewed and will be divided into cancer-related and non-cancer related diarrhea. Although many of the references in this summary refer to the immediate release form of Sandostatin®, the more recent, long-acting formulation, Sandostatin® LAR®, has shown the maintenance of all clinical and pharmacological characteristics of the immediate form whilst having the added profile of slow release (over 28 days) at the site of administration through biodegradation of the polymer containing the active drug. Mostly, once steady-state levels have been achieved, a 20 mg intramuscular dose of Sandostatin® LAR® every 4 weeks produces the same pharmacological effects as 150 µg Sandostatin® by SC injection three times daily (tid) (9,13).

They state that most patients with mild symptoms should see a decrease in the frequency and quantity of bowel movements within 24 hours at the recommended dose of 100-150 µg every 8 hours

In some indications such as dumping syndrome a different effect might be noticed with Sandostatin® LAR® vs Sandostatin® subcutaneously.

1.0 The use of Sandostatin® in cancer- related diarrhea

There are many treatment-related factors that can contribute to diarrhea in cancer patients, including damage to and maturational arrest of intestinal epithelium, inflammation, and/or infection. Although the pathophysiological mechanisms for cancer treatment-related diarrhea have not been elucidated fully, histopathological evidence indicates that it is a multifactorial process resulting in absorptive and secretory imbalances in the small bowel, the specific mechanisms differ among cancer patients depending on the causative factor (14,15).

Mucositis is a major problem in cancer patients, occurring in approximately 40% of patients undergoing standard dose chemotherapy and in almost all patients undergoing high dose chemotherapy and stem cell or bone marrow transplantation (16-18). It is caused by the cytotoxic effect of chemo- and/or radiotherapy and affects the entire length of the GI tract. It causes a number of symptoms, including both diarrhea and constipation.

Sandostatin® administration – both SC and LAR – has been found to improve mucosal injury and chronic structural changes caused by radiation insults in the rat ileum (19) and has shown promise in initial clinical testing (20). Other causes of diarrhea in the cancer patient include the underlying cancer (carcinoid syndrome, colon cancer, lymphoma, medullary carcinoma of the thyroid, pancreatic cancer), concomitant diseases, responses to dietary intake or the stress and anxiety associated with the cancer diagnosis and treatment (20,21).

One study, designed to investigate the effectiveness and improvement in the quality of life of cancer patients taking Sandostatin® LAR® administered for the treatment of loperamide-refractory diarrhea not attributed to medical therapy, reported that the administration of Sandostatin® LAR® at a starting dose of 30 mg every 28 days effectively resolved or controlled the diarrhea (20). Twenty-three patients (79.3%) achieved resolution, six patients (20.7%) successfully controlled their diarrhea and all patients had improved sodium, potassium, albumin and total protein values and quality of life values.

Treatment-related diarrhea

1.1. Chemotherapy-induced diarrhea (CID)

Cytotoxic chemotherapy commonly causes severe diarrhea as a side effect. This is particularly the case if the chemotherapy regimens contain 5-fluorouracil (5-FU) and is frequently severe enough to require a dose reduction, a delay or discontinuation of the cancer treatment with possible adverse effects on patient outcome.

The United States Cancer Institute (NCI) Common Toxicity Criteria classifies diarrhea into four different

grades (1–4) based on the number of stools produced per day, the degree of incontinence or presence of blood in the stools and the degree of cramping or need for intravenous fluid support (22).

Diarrhea-associated mortality is reported as high as 3.5% in clinical trials of bolus 5-FU and irinotecan in colorectal cancer. Although well established, the frequency of CID and its impact on patient management are frequently under recognized in clinical practice (23). One study has reported that 50-80% of patients treated with irinotecan and 26-56% of those treated with 5-FU developed diarrhea (24). Earlier studies have put this occurrence rate between 23-52% (24-28). On the contrary, we must recognize that the combination of 5-FU/Leucovorin and irinotecan causes less intense diarrhea than irinotecan alone. In 2004, the American Society of Clinical Oncology proposed Sandostatin® as curative treatment in gr III and IV CID in their guidelines (29). A Canadian Working Group recommended even to prevent and manage CID in all of its grades of severity

- The first-line choice should be loperamide or diphenoxylate.
- Subcutaneous Sandostatin® is recommended for refractory grade 2 diarrhea and also for grade 1 CID, which remains intractable with high-dose loperamide.
- Patients with grades 3 and 4 CID should be managed with hospitalization, including rehydration, antibiotic therapy and Sandostatin®.
- A reduction in chemotherapy dose is recommended for patients with a history of grade 3 or 4 CID in a previous cycle of chemotherapy. Prophylactic use of Sandostatin® LAR® may be considered if reducing the chemotherapy dose is not desired, eg in adjunct and neoadjuvant settings (23).

Recently, a nice overview was published by Bhattacharya S *et al.* (30).

In the prevention and treatment of CID, clinical trials have demonstrated that Sandostatin® (100-150 μg SC tid) is effective in resolving grades 3 and 4 diarrhea in 60-95% of patients after chemotherapy (31,32,33) or pelvic radiotherapy (31). A higher dose of 500 μg has been shown to be well tolerated (31) and more effective in resolving intractable diarrhea in chemotherapy patients (31,33), which has led to an analysis of the cost-benefit ratio of this treatment when compared to the time needed for hospitalization.

In a Phase I trial investigating the effects of Sandostatin® in the range of 50-2500 μg (SC tid) for 5 days, 35 patients received 49 courses of therapy (35). The maximum-tolerated dose was 2000 μg with one patient experiencing an allergic reaction with flushing, nausea and dizziness after each of the first two injections with 2500 μg. The efficacy of treatment was reported to correlate significantly with the dose of Sandostatin® administered (P=0.001) and more patients completed the course of 5-FU therapy at the higher doses (35).

In previous guidelines, published in 2004, the dose of Sandostatin® is recommended to be increased by increments of 50 μg in patients who do not respond (29). However, basing their advice on clinical practice rather than data from clinical trials, the Canadian Working Group recommended a dose escalation to 300-500 μg SC tid until the diarrhea resolves (23).

No recommendations for prophylaxis are given in the current guidelines, although they do state that the prophylactic management of patients is necessary. A preliminary study has reported that 150 μg Sandostatin® tid in conjunction with 5-FU was not effective in adult cancer patients (31). Out of ten patients undergoing treatment, two experienced dose-limiting diarrhea and only three patients were able to tolerate the six weekly chemotherapy treatments without dose reduction or delay.

However, the prevention of diarrhea through the prophylactic use of Sandostatin® LAR® is a strategy still currently under investigation (31).

Sandostatin® LAR® has been reported to be effective in a small series of patients with colorectal cancer who developed severe refractory diarrhea after fluoropyrimidine or irinotecan chemotherapy (31-33). These patients, all unresponsive to loperamide and/or diphenoxylate, were successfully treated with Sandostatin® LAR® (30 mg), which caused all diarrhea to be resolved with no further hospitalization required.

Retrospective case reports of the use of 20-40 mg Sandostatin® LAR® in patients with CID refractory to conventional antidiarrheal therapy show that the majority of treated patients experienced resolution to grade 0 or 1 diarrhea and were able to continue chemotherapy at full dose with only minimal side-effects (39-41). One study reported that Sandostatin® LAR® 30 mg was effective for the control of loperamide-refractory diarrhea and for the prevention of further episodes of diarrhea following continuation of chemotherapy (41) and another report of three case studies suggested the benefit of using 30 mg Sandostatin® LAR® as a secondary prophylactic agent to shorten the duration of diarrhea, improve patient quality of life, allow continuation of chemotherapy without further suspension or dose modification because of GI toxicity and to avoid the need for expensive hospitalization (40).

Based on current research, Sandostatin® LAR® (30 mg) can be an option for the treatment of diarrhea in colorectal cancer patients who have experienced grade 3 or 4 diarrhea in a previous course of chemotherapy.

Due to the promising effects of Sandostatin® LAR® and the suggestions that Sandostatin® dose escalation was sometimes necessary for optimal control of CID in the literature, the STOP trial (Sandostatin® LAR® Depot Trial for the Optimum Prevention of Chemotherapy-Induced Diarrhea) was designed to investigate the effects of 30 mg and 40 mg Sandostatin® LAR®. In this open-label, randomized, parallel group, multicentric study, 147 patients received six doses of either dose level. Results showed that fewer patients in the 40 mg group

experienced severe diarrhea, when compared to the 30 mg group (61.7% vs. 48.4%; $P = 0.14$).

Fewer patients receiving the 40 mg dose also needed less IV fluid supplementation and less unscheduled healthcare visits. However, none of these results were statistically significant and no significant differences were recorded in the treatment groups' measured quality of life, or treatment satisfaction. Therefore, based on this trial alone, no specific recommendation can be made on the benefits of 40 mg over 30 mg Sandostatin® LAR® for CID (31).

In one study, 59 patients with colorectal and head and neck carcinoma, with 5-FU-induced diarrhea refractory to loperamide, were enrolled in two arms of a trial designed to investigate the therapeutic benefit of Sandostatin®. Results supported the dose-response effect of Sandostatin® with complete diarrhea resolution in 60.71% of patients treated with 100 μg and 90.32% of patients treated with 500 μg, both arms receiving the dose subcutaneously three times daily (33).

Another study, comparing the higher dose of 500 μg Sandostatin® with loperamide (4 mg tid) in patients receiving modulated 5-FU regimens demonstrated a significant improvement in the rate of diarrhea resolution after four days (80% vs 30%; $P < 0.001$) (32).

Severe diarrhea has a dose-limiting effect on irinotecan therapy. One preliminary study, performed on four subjects with metastatic GI tumors with diarrhea refractory to opioids, showed promising results with all patients displaying complete resolution of diarrhea within 2-4 days of Sandostatin® treatment (either subcutaneous every eight hours or by continuous subcutaneous infusion) (31). A dose of 500 μg tid has also been reported to be effective in patients with loperamide-refractory diarrhea whilst receiving irinotecan (36). Prospective studies are warranted to determine the reactions of patients to the longer-acting Sandostatin® LAR® formulation.

1.2. Radiotherapy (RT) – induced diarrhea

Pelvic radiation therapy (RT) is used in a number of indications, either as an adjuvant or primary treatment for patients with gynecologic, genitourinary, GI and other cancers. Small bowel tolerance to this treatment is a dose-limiting factor due to early adverse effects (44). Pelvic or abdominal RT is known to cause acute enteritis, characterized by abdominal cramping and diarrhea, in approximately 50% of treated patients and the incidence is higher with concomitant chemotherapy (45,46). At present, there is no clear pharmacologic strategy for effective prevention of RT-induced diarrhea. Standard medical treatment for acute radiation-induced diarrhea (ARID) has included nonspecific agents including the opium preparation paregoric, opioids diphenoxylate, atropine and loperamide (47,48).

However, both clinical and preclinical investigations with Sandostatin® have provided some promising results. Preclinical data supporting the potential use of Sandostatin® in the indication of RT-induced diarrhea include the fact that its administration effectively reduced acute mucosal changes as well as subsequent chronic structural changes following irradiation of exteriorized small bowel such as mucosal atrophy, intestinal wall thickening and fibrosis (49-50).

Although oral opiates including loperamide and diphenoxylate, are effective in the majority of cases, a randomized trial comparing Sandostatin® (100 μg tid) with oral diphenoxylate (10 mg/d) in 61 patients with grade 2 (4-6 stools per day) or 3 ($\geq$ 7 stools per day) diarrhea has found that Sandostatin® is significantly more effective than oral opiates, with 61% of patients treated with Sandostatin® experiencing complete resolution within three days of treatment compared to only 14% of patients treated with diphenoxylate ($P < 0.002$) (51). Another advantage of the use of Sandostatin® in this trial was the reduction in duration of interruptions in the course of radiotherapy when compared to the diphenoxylate arm, with a mean of 0.5 days vs. 2.0 days, respectively (34). However, the promising results from this randomized, controlled study with GI patients was investigated further and the North Central Cancer treatment Group performed a phase III double-blind trial to compare the prophylactic effects of Sandostatin® LAR® with placebo in the patients undergoing pelvic radiation therapy (52).

One hundred and twenty five evaluable patients were randomly allocated to receive Sandostatin® or placebo at the start of the radiation. Sandostatin® treatment involved 100 μg SC on day 1, followed by intramuscular (IM) Sandostatin® LAR® (20 mg) on days 2 and 29. This study reported that diarrhea of severity grades 0, 1, 2 and 3 occurred at similar frequencies in both the treatment and placebo arms ($P = 0.04$) and concluded that the treatment regimen of Sandostatin® in this trial did not provide a prophylactic advantage (52). The study does not exclude the possibility, however, that octreotide might benefit a more homogeneous group of patients. Today, there is no place for general use of depot octreotide in the prevention of radiation-induced acute diarrhea.

1.3. Chemoradiotherapy (CRT) – induced diarrhea

Chemotherapy in conjunction with radiotherapy improves both local control and survival in patients with advanced rectal carcinoma (53,54). However, this adjuvant chemoradiotherapy (CRT) can lead to an aggravation and accumulation of side effects. Diarrhea following CRT can cause severe fluid, mineral and protein losses, which can lead to decreased patient compliance and treatment delays (55).

The current antidiarrheal treatment for CRT-induced diarrhea includes nonspecific agents such as loperamide, diphenoxylate, codeine or the opium preparation paregoric and nutritional support (47,56). However, these

agents are frequently ineffective in controlling the patient's diarrhea (57).

A prospective pilot study designed to evaluate the efficacy of Sandostatin® in the treatment of CRT-induced diarrhea, refractory to loperamide, in rectal carcinoma patients treated with pelvic radiotherapy in conjunction with weekly 5-FU treatment reported that Sandostatin® (150 μg SC tid) was highly effective as a second-line antidiarrheal treatment. Of the 42 rectal carcinoma patients with grade 2 or 3 diarrhea refractory to loperamide, 34 patients (80.9%) experienced complete resolution in a mean of 2.7 days following Sandostatin® administration. Twenty-seven patients (64%) responded during the first three days and the remaining seven (17%) on days four and five, with no significant side effects (31). Thus, the investigators reported that using Sandostatin® in the above approach for at least three days (preferably five days) could lead to a minimization of treatment delays and achieve better results with CRT. Future research investigating higher doses of Sandostatin® in larger patient groups will help confirm this treatment strategy.

A recent randomized, double-blind, placebo-controlled phase III study with 233 patients was conducted to investigate the efficacy of Sandostatin® LAR® in preventing or reducing the severity of CRT-induced diarrhea in patients with anal or rectal cancer (59). The study analyzed the responses from 215 patients and found that there was no significant difference between the incidence of grade 2 or above diarrhea (P=0.21) with 52 (49%) and 48 (44%) in the placebo and Sandostatin® LAR® treatment arms, respectively. This study thus concluded that the prophylactic use of two 30 mg doses of Sandostatin® LAR® was not able to significantly reduce the incidence of mild, moderate or severe diarrhea.

The benefit of Sandostatin® treatment in CT or CRT induced refractory diarrhea is clear. Although in the setting of prevention, no clear answer is given by the current available studies.

Disease-related diarrhea

1.4. Neuroendocrine tumor (NET) carcinoid syndrome

Carcinoid tumors mainly originate from the cells in the gastric or small intestinal mucosa and pancreas, but can also arise from the ovaries or lung tissue (60). Sandostatin® has been registered in most countries for the control of hormonal symptoms in patients with GI and pancreatic neuroendocrine tumors [NETs], as well as in patients with acromegaly (61).

The most common symptoms of carcinoid tumors are collectively referred to as carcinoid syndrome and are elicited by the excessive secretion by metastatic tumors of major regulatory vasoactive peptides and amines, such as serotonin and its metabolites, VIP and bradykinin (62, 63) that result in cutaneous flushing, diarrhea and bronchospasm.

Due to the drug's potent antisecretory effects, Sandostatin® is one of the few cancer drugs that is continued in the face of tumor progression and can be used with other treatment modalities without additional toxicity (61).

Octreotide acts by inhibiting release of 5HIAA, release of VIP and 5-HT. In its short-acting form, Sandostatin® has been reported to relieve both the diarrhea and flushing associated with carcinoid syndrome. In one study, it induced symptomatic and biochemical responses in 40% to 70% of patients (64) and symptom control may last for months (65). A prospective, randomized trial investigated the efficacy of the more convenient Sandostatin® LAR® in a dose of 10 mg, 20 mg or 30 mg every four weeks against an open-label subcutaneous dose (identical to that received during screening) every 8 hours (9). This study found that, once the steady-state concentrations are achieved, Sandostatin® LAR® controls the symptoms of carcinoid syndrome at least as well as the short-release subcutaneous form of Sandostatin®.

The median number of daily stools decreased significantly from baseline levels in all treatment groups. No dose-response relationship was observed in the incidence or severity of adverse events and Sandostatin® LAR® was found to have a comparable efficacy to the subcutaneous form of Sandostatin® with a similar safety profile and is a valid alternative to the short-acting form. The authors of the trial report conclude that Sandostatin® LAR®, with the availability of the once-monthly injection has the potential to increase the number of patients willing to undergo treatment and therefore improve patient compliance and satisfaction with therapy, leading to a successful clinical control of the carcinoid syndrome (9).

A starting dose of 20 mg LAR octreotide is recommended (67). There is some evidence for a dose-response relationship in the treatment of neuroendocrine tumors (66).

Sandostatin® LAR® is worldwide accepted as symptomatic therapy for the treatment of functional gastro-entero-pancreatic endocrine tumours and indicated for carcinoid tumours with carcinoid syndrome, VIP-tumours, glucagonoma, gastrinoma with syndrome of Zollinger-Ellison syndrome, insulinoma and GRF-tumours.

Tumors originating from pancreatic non-beta islet cells frequently secrete high levels of vasoactive intestinal peptide (VIP) and cause a severe form of secretory diarrhea. The intensity of these symptoms fluctuates but can be so severe that patients produce an excess of five liters of stool per day.

Guidelines for using Sandostatin® to control secretory diarrhea in this condition are identical to those for carcinoid tumors and Sandostatin® should be initiated at 100-150 μg (SC tid) and patients monitored on a daily or weekly basis, depending on symptom severity (60). The Consensus Panel notes that Sandostatin® may actually exacerbate the symptoms of diarrhea at low doses

($\leq$ 25 µg) due to the prokinetic effect of Sandostatin® on GI motility. In these cases, it is recommended to increase the dose until adequate symptom control is achieved.

The gold standard in pharmacological treatment are somatostatin analogs which can induce long-term remission, even in inoperable lesions (68).

2.0. The use of Sandostatin® in non-cancer-related diarrhea

2.1. Short bowel syndrome (SBS)

Short bowel syndrome (SBS) has been defined as 'an impairment of absorptive capacity necessitating prolonged fluid and/or nutritional support' (69). This includes patients who have an anatomically short small intestine, either as a result of massive intestinal resection or a functionally short small intestine as a result of severe mucosal disease, such as Crohn's disease or radioenteritis. Most patients with SBS either have a high jejunostomy with a residual jejunal length of $<$ 100 cm or a jejunocolic anastomosis.

SBS is characterized by the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balances when on a conventionally accepted, normal diet (70). Extensive resection of the small intestine results in a malabsorptive state. In the majority of adult patients, Crohn's disease is the etiology. Congenital abnormalities such as gastroschisis and necrotizing enterocolitis may also result in SBS. The goal in managing patients with SBS include maintenance of nutrition and hydration to correct specific deficiencies, control the diarrhea, promote intestinal adaptation and prevent any metabolic complication.

Pharmacologic management of SBS, as an adjunct to dietary interventions, involves the use of antimotility and antisecretory agents (70). Sandostatin® has been used in the management of diarrhea in patients with this condition due to its antimotility effects prolonging contact of luminal contents with the intestinal mucosa and decreased pancreatic and biliary secretions. It has also been shown that Sandostatin® prolongs small-bowel transit time and reduces ileocolonic bolus transfer in healthy subjects (71).

It has been suggested that Sandostatin® can be used to decrease the secretory diarrhea in order to reduce the need for electrolyte and fluid replenishment, but should only be used if the requirements are more than 3 liters per day, due to the risk of cholelithiasis and impaired intestinal adaptation (72,73). This latter risk is based on animal models of SBS that suggest Sandostatin® may impair intestinal adaptation by decreasing the secretion of trophic factors (74-76).

One case report notes the failure of a patient, with a small bowel length of 70 cm, to respond to Sandostatin® (50 µg, bid) (77). However, once the Sandostatin® LAR formulation® (20 mg) was administered, the patient's abdominal cramping and diarrhea resolved (78).

A prospective, open trial of Sandostatin® LAR® (20 mg) in the management of SBS investigated the drug's effects on stool water and electrolyte losses, fecal fat excretion and GI transit in SBS patients needing total parenteral nutrition (79). Eight patients were included and it was reported that Sandostatin® LAR® use for 15 weeks significantly prolonged the small bowel transit time with no effect on gastric emptying rate. Although a favorable trend was also recorded in increasing body weight, decreased stool weight and reduced fecal sodium excretion, these values were not statistically significant.

It can be expected by an increase in duration of the transit time that contact of nutrients, fluid and electrolytes with the mucosa increases. This results in a facilitation of the absorption. Further controlled, dose-response trials are therefore required to assess the optimal frequency of administration and evaluation of dosage for the various factors that affect SBS.

2.2. Ileostomy and jejunostomy

End-jejunostomy syndrome (EJS) is an extreme form of SBS in which the majority of intestinal absorptive function is lost while gastric, pancreatic and biliary secretion remain intact. This leads to high losses of macronutrients, fluid and electrolytes through the stoma and may result in rapid dehydration and electrolyte imbalance and death.

A case of a patient presenting with persistent ileostomy-related diarrhea, unresponsive to conventional dry treatment and which necessitated parenteral nutrition has been reported (77). The patient was administered Sandostatin® (50 µg SC bid), which dramatically reduced the life-threatening diarrhea and improved the patient's quality of life. Due to the presentation of symptoms and levels of water and electrolytes in the effluent it was thought that secretory, malabsorptive and osmotic factors appeared the cause. The patient was successfully treated with Sandostatin®.

In a study with 12 high-output proximal ileostomy patients were treated with Sandostatin® (100 µg), it was reported that the level of stoma output with concomitant daily loss of electrolytes was reduced with easily tolerated mild side effects (81).

Short-acting Sandostatin® (100 µg, tid) was assessed as an adjunctive therapy to home parenteral nutrition in the management of ten patients with adapted EJS. It was reported to be effective in decreasing the IV fluid and electrolyte requirements in patients with end-jejunostomy (81). The response to Sandostatin® was immediate and resulted in a major improvement in the quality of life of these patients. This beneficial effect was seen to continue over time during the long-term follow-up observations of open treatment for greater than one year.

The most important side effect to be considered in these patients is the potentiation of subacute intestinal obstruction. Many patients with end-jejunostomies, particularly those with Crohn's disease, have had numerous

operations and are at high risk of mechanical obstruction due to adhesion. Sandostatin's potent antimotility effect may exacerbate this situation and its inhibitory effect may aggravate gallbladder disease due to biliary stasis (84). Therefore, further studies are required on larger patient populations before this drug can be recommended for use in this group of patients.

Sandostatin®'s potential to adversely affect protein metabolism by reducing pancreatic enzyme secretion, possibly by inhibiting the uptake of amino acids by the exocrine pancreas for enzyme synthesis (83), has been studied in nine patients with permanent jejunostomies (82). In comparison with normal, healthy controls, the baseline measurements of amino acid metabolism were normal in patients with EJS on home parenteral nutrition, but pancreatic enzyme synthesis and secretion were elevated. Sandostatin® (100 μg SC tid) improved fluid balance but was found to suppress gut hormone levels in the blood and also uptake of amino acids into pancreatic enzyme and mucosal proteins, thereby increasing oxidative losses. The authors concluded that further studies are necessary to assess whether the results obtained in this small sample size are clinically relevant in the long-term management of patients with jejunostomies (82).

The subcutaneous, short-acting form of Sandostatin® has also been used as a form of 'hormonal' ileostomy or protective colostomy for ulcerative colitis or obstruction of the left colon due to carcinoma or diverticulitis (85). In these patients, Sandostatin® caused a favorable delay in peristalsis return on the third to fifth postoperative day ; peristalsis returned early on the second day in only one patient.

The Sandostatin® effect at long term on stomal effluents in patients with severe short bowel syndrome was investigated in a double blind placebo controlled balance study (87). Five patients had a jejunostomy and one an ileostomy. Subcutaneous injections of 50 μg every 12 hours had a similar effect on net intestinal absorption of sodium and water as parenteral nutrition. In an open follow up study of five to six months, subcutaneous octreotide in the same doses was administered by the patients at home. The effect on faecal sodium loss persisted, except for one patient. It decreased net absorption of water and sodium following reduced secretion of digestive juices rather than by increasing absorptive capacity. Sandostatin® may be useful as antidiarrheal drug in patients with high output jejuno- or ileostomies, but in patients who need permanent parenteral nutrition the effect is too small to significantly alter management.

2.3. Dumping syndrome

Dumping syndrome is a serious complication occuring mostly after esophageal or gastric surgery, and since bariatric surgery it has become the principal cause of postoperative dumping. The clinical picture consists of two phases, namely early and late dumping, which may be present simultaneously or separately. Early dumping is the result of rapid nutrient delivery into the small intestine and is characterized by abdominal symptoms such as diarrhea, nausea, fullness and abdominal cramps. In addition, systemic vascular changes result in palpitations, headache and the wish to lie down. Late dumping occurs 1-3 hours postprandially and is merely the result of reactive hypoglycemia. Symptoms of late dumping are transpiration, tremor, dizziness and hunger (88).

Treatment of dumping syndrome and diarrhea depends on the severity of symptoms and can be achieved in the majority of cases through dietary and lifestyle modifications, such as reducing the patient's carbohydrate intake. In more severe cases, additional treatment with acarbose (89) or guar gum or pectine (90) might be necessary. However, severe symptoms can persist despite dietary changes in 3-5% of dumping syndrome sufferers.

These refractory symptoms can improve with daily subcutaneous injections with octreotide (91). Several short-term studies with subcutaneously administered octreotide have documented efficacy in improving symptoms, glycemias and slowing gastric emptying (92-95).

In a double blind placebo controlled crossover trial with one week wash-out the effects of Sandostatin® 50 μg before ingesting 75 g glucose were studied in eight patients (92). Follow-up was set at 180 minutes and Sandostatin® was found to have a highly significant effect on diarrhea ($p < 0{,}001$) with no observed side effects.

The long-acting formulation of octreotide has been successfully used in the treatment of dumping syndrome. Sandostatin® LAR® is able to slow gastric emptying rate, to slow small bowel transit, to inhibit the postprandial release of gastrointestinal and metabolic hormones such as insulin, gastrin, pancreatic polypeptide, cholecystokinin, glucagon, neurotensin and secretin and to inhibit insulin secretion, and to inhibit postprandial vasodilation (96,97). Both short- and long-acting octreotide have been used in the treatment of dumping syndrome.

In a recent study 30 dumping patients after different types of surgery were treated with Sandostatin® SC and LAR. Sandostatin® improved early and late dumping symptoms. Sandostatin® LAR® had less effect on late dumping (98). Steatorrhea as a side effect was reported by several patients in the present study, which may in part be attributable to the inhibitory effect of octreotide on human exocrine pancreatic and biliary secretions.

A randomized study is ongoing and these results are necessary before we recommend Sandostatin® LAR® in daily practice for the treatment of refractory dumping as a guideline.

2.4. Graft versus Host Disease (GVHD) diarrhea

Diarrhea associated with Graft Versus Host Disease (GVHD) is considered to be a classic example of secre-

tory diarrhea, characterized by a voluminous secretion of fluids and electrolytes. Patients with GVHD of the GI tract experience an immune reaction that attacks the cells lining the GI tract. In the very early stages, these cells are destroyed, resulting in crypt cell necrosis. After approximately 10-14 days, complete denudation of the GI tract can occur, resulting in secretory diarrhea. This diarrhea can occur despite early and aggressive immunosuppressive therapy and the massive loss of gut epithelium requires 4-8 weeks to heal.

Histological damage to the intestinal mucosa in patients with GVHD is similar to the damage caused by cancer treatment although the pathophysiology is different (14). Management of patients with GVHD of the intestine presents a formidable enormous challenge. It is characterized by profuse watery diarrhea, which can be up to 15 liters per day, abdominal pain, nausea, vomiting and GI bleeding. The severe diarrhea may contribute to high morbidity through malnutrition and large losses of water, electrolytes and proteins in the stool in addition to infectious complications (99-101).

In a pilot study, six patients with acute gut GVHD following allogeneic bone marrow transplantation, received Sandostatin® (50-250 µg SC tid) (102). Three patients had a prompt and dramatic reduction in stool volume and frequency within one to three days of treatment and three patients failed to respond. The three non-responders could have been due to persistent and ongoing injury to the gut mucosa of these patients. In another study, five patients with acute intestinal GVHD were treated with Sandostatin® (250 µg) and complete diarrhea control was observed in three. The other two patients died due to progressive hepatic failure due to an acute GVHD of the liver (103). Also a patient with GVHD-like colitis resulting from T-cell dysregulation by a malignant thymoma, was given Sandostatin® to treat her severe diarrhea, which subsequently improved.

In another pilot study, 21 patients were included and given Sandostatin® (500 µg IV tid) (104). Fifteen (71%) of the treated patients achieved a complete response within seven days of initiation and three (14%) failed to respond. The authors of the study concluded that, if initiated early in the course of GI GVHD, Sandostatin® appears to be an effective, well-tolerated treatment to reduce severe voluminous diarrhea in a high percentage of patients (104). A previous report of the unsuccessful use of Sandostatin® to control diarrhea in GVHD patients may have been due to the later time of treatment initiation (105). It is therefore recommended that Sandostatin® should be administered early in the course of GVHD as soon as diarrhea onset is noted and should be discontinued upon resolution to avoid constipation and the potential development of an ileus (106).

In the first reported case of the use of continuous Sandostatin® infusion for the treatment of GVHD-related diarrhea in a 22-month-old child, Sandostatin® was initially given at 30 µg (2 µg/kg IV tid) and then escalated to continuous infusion at 15 µg (1 µg/kg/h) (107). The child's symptoms of profuse diarrhea with bloody stools were promptly resolved with the moderate use of Sandostatin®. The diarrhea rebounded upon cessation of the therapy, but resolved once more when the dose of Sandostatin® was escalated during a 48h period to 15 µg/h (1 µg/kg/h or 360 µg/day) and maintained for 7 days (107). These documented effects of Sandostatin® in GI GVHD-related diarrhea reflect a novel approach to GVHD therapy (108).

Guidelines state that the pharmacologic approach to GVHD-induced diarrhea should include continuation of therapy with immunosuppressants, the addition or increase of corticosteroids and Sandostatin® (500 µg IV tid) (99). The patient's response to Sandostatin® should be continued for a maximum of seven days. Second-line immunosuppressive therapy should also be added to the treatments if the corticosteroid treatment fails to elicit a response within 3-4 days of initiation.

At the time of publication of these guidelines, Sandostatin® LAR® is under investigation of its potential benefit in prophylaxis.

2.5. AIDS-related diarrhea

More than one hundred million people worldwide are currently infected with the human immunodeficiency virus (HIV) and a substantial number of these individuals will suffer from diarrhea. In the United States, it is known that around 50% of HIV-infected individuals suffer from diarrhea (109). In the developing world it probably is as high as 80% of patients.

The clinical presentation of AIDS-related diarrhea varies among patients. Small-bowel diarrhea produces voluminous postprandial stools with accompanying abdominal pain. Large-bowel diarrhea, also known as colitic diarrhea, is associated with frequent, small volume stools.

The major identified causes of AIDS-related diarrhea are *Cryptosporidium* and *Microsporidium* protozoa, but enteric pathogenic bacteria, mycobacteria, viruses and fungi can also play a significant role.

Chronic diarrhea may contribute significantly to the morbidity and mortality of the disease. A number of uncontrolled studies evaluating the efficacy of Sandostatin® to control diarrhea in AIDS patients have been published (110-118). These studies ranged in size from 4-129 patients and have demonstrated a response rate of 25-45%.

In one study, 12 consecutive HIV seropositive patients with chronic refractory diarrhea were recruited and small intestinal motility was measured continuously for 48h (119). During the second 24h period, Sandostatin® was administered (100 µg SC tid) and small bowel pressure was recorded and subjects were asked to keep a log. The results of this trial demonstrated that Sandostatin® increased the number of migratory motor complexes (MMCs) in the small bowel and contraction frequency was significantly reduced. Thus, Sandostatin® was found

to have a significant effect on small intestinal motility in HIV-infected patients with diarrhea, which may influence the intestinal transit.

Several controlled studies have also been conducted to evaluate the therapeutic effect of Sandostatin® in AIDS-related diarrhea, but with mixed results (120-122). Unfortunately these studies are of limited value due to a number of criticisms in either trial design (120,121) or due to a lack of control of patient compliance, patient population heterogeneity or lack of a standardized patient diet (122,123).

One particular double-blind, placebo-controlled trial randomized 129 subjects to receive Sandostatin® 100 µg, 200 µg or 300 µg (sc tid) or placebo (122). Although differences between the groups were noted, they weren't statistically significant. Subjects who received Sandostatin® achieved control of their diarrhea by the end of the study in 48% of cases, compared to 39% of subjects in the placebo group. At 300 µg, 50% of the patients achieved diarrhea resolution compared with 31% of control subjects. However, when the trial was extended for 8 weeks during the open label phase, a significant reduction in the overall stool frequency was noted, from a mean of ~7 stools per day to ~4 stools per day (122).

Although promising results have been seen with the aforementioned trials, the published data can't be used to support the routine use of Sandostatin® in the treatment of AIDS-related diarrhea. Future trials are needed and should improve upon previous trial designs by including homogenous patient populations with a standardized diet, a thorough check of patient compliance, testing high doses of Sandostatin® and having a sufficiently long duration to evaluate the effects of the treatment.

3.0. Conclusions

Sandostatin® has been used and tested for the treatment of (refractory) diarrhea from different etiologies. It has been shown to be effective in the control of diarrhea associated with carcinoid syndrome, vasoactive intestinal polypeptide (VIP) tumors, dumping and short-bowel syndrome. It is recommended for use in severe (grades 3-4) chemotherapy-induced diarrhea refractory to opioids and has also been effective in diarrhea associated with GVHD. Based on comparable activity, mostly the long-acting formulation is used in clinical practice. This formulation is convenient for the patients and has in general limited side effects.

Although the reported studies underbuild the consensus guidelines for the use of Sandostatin® for refractory diarrhea (60), further evidence-based support is required. Large-scale, comparative clinical trials of sufficient power are needed to define both the optimal dosage and efficacy of Sandostatin® in comparison with conventional therapy in the treatment of cancer, and non-cancer related diarrhea. These well-designed trials should define the place of Sandostatin®.

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