Colon polyps in patients with short bowel syndrome before and after teduglutide: post hoc analysis of the STEPS study series

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Abbreviations: ACS, American Cancer Society; IBD, inflammatory bowel disease; NA, not applicable; NR, not reported; PBO, placebo; SBS–IF, short bowel syndrome and intestinal failure; STEPS, Study of Teduglutide Effectiveness in Parenteral Nutrition-Dependent Short Bowel Syndrome Subjects; TED, teduglutide

Highlights:

- Post hoc analysis on colon polyps in patients with SBS-IF from the 3 STEPS studies
- Data from colonoscopies before and after 24–36 months treatment with teduglutide
- Baseline colonoscopy detected and removed colorectal polyps in 9 (12%) patients
- Colorectal polyps detected in 9 (18%) patients, 2 (22%) of whom had baseline polyps
- Supports prescribing recommendations for colonoscopy before and during teduglutide

Abstract

Background & Aims: Teduglutide, a GLP-2 analogue, promotes intestinal growth and is approved for the treatment of short bowel syndrome and intestinal failure (SBS-IF).[1,2] Colonoscopy is recommended before and after teduglutide therapy but there are few data on the development of colorectal polyps in this population. The aim of this study is to report the occurrence of colorectal polyps in adult patients with SBS-IF who received teduglutide in clinical studies conducted to-date.

Methods: A post hoc analysis of the completed Study of Teduglutide Effectiveness in Parenteral Nutrition-Dependent Short Bowel Syndrome Subjects (STEPS) clinical study series **(NCT00798967, EudraCT 2008-006193-15; NCT00930644, EudraCT 2009-011679-65; NCT01560403)** evaluated electronic case report form data for baseline colonoscopies (performed before treatment) and for surveillance or end-of-study (performed after treatment with teduglutide **0.05 mg/kg/day** for 24 and 36 months) procedures.

Results: Of the 98 patients in the STEPS studies population, 73 patients had a baseline colonoscopy and 50 patients had a surveillance/end-of-study colonoscopy. Colon polyps were reported at baseline in 12% (9/73) of patients **and a**t the surveillance/end-of-study in 18% (9/50) of patients. Of these patients, **two had polyps both at baseline and at the** surveillance/end-of-study. Histology, available for seven samples, reported no malignancy. One patient had **serrated** and 4 patients had tubular adenomas.

Conclusion: These data support recommendations for colonoscopic screening before teduglutide therapy and subsequent on-therapy colonoscopic surveillance, for patients with SBS-IF. Further studies are required to assess the risk of polyp formation in these patients with SBS-IF and the most appropriate colon polyp surveillance strategies.

Keywords: clinical; colon; adenoma; polyp; risk; surveillance

Introduction

Teduglutide, an analogue of glucagon-like peptide 2, is approved for the treatment of patients with short bowel syndrome (SBS) dependent on parenteral support.[1,2] Based on the pharmacologic activity and preclinical findings, teduglutide has the potential to cause hyperplastic changes.[1,2] The prescribing information and product monographs recommend that patients have colonoscopy of the entire colon with removal of polyps before the initiation of treatment with teduglutide and follow-up colonoscopies during treatment.[1,2] This brief communication reports data from three completed adult studies in the Study of Teduglutide Effectiveness in Parenteral Nutrition-Dependent Short Bowel Syndrome Subjects (STEPS) clinical trial series[3-5] for all patients who underwent colonoscopy and had polyps at baseline or during subcutaneous administration of teduglutide 0.05 mg/kg/day.

Material and methods

This post hoc analysis included all individual colonoscopy data from the double-blind, placebo-controlled STEPS (NCT00798967; EudraCT 2008-006193-15) study[3] and its two open-label extension studies; STEPS-2 (NCT00930644; EudraCT 2009-011679-65),[4] and STEPS-3 (NCT01560403).[5] The flow of patients across the STEPS clinical trial series has been published in Seidner et al.[5] Patients were eligible to participate in STEPS if they had SBS–IF caused by a major intestinal resection, were parenteral support dependent for ≥12 months before signing informed consent, and required parenteral support ≥3 times weekly. Patients in STEPS-2 and -3 met the same criteria; patients in STEPS-2 had to have completed 24 weeks of treatment (teduglutide or placebo) in STEPS[4] and patients in STEPS-3 had to have completed 24 months of teduglutide in STEPS-2[5]. All patients had provided written informed consent for study participation. All studies were conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation and Good Clinical Practice, and were approved by local institutional review boards/independent ethics committees/research ethics boards.

The study protocol required a baseline colonoscopy for all patients with colon-in-continuity and requested that polyps or active intestinal disease be ruled out in patients with remaining colon. The colonoscopy was performed at the end of the parenteral support stabilization period (baseline study visit) and before randomization. Patients who had a normal colonoscopy within six months of their screening visit were not required to undergo another colonoscopy. All benign gastrointestinal polyps had to be removed before randomization for patients to be eligible for enrollment. An end-of-study colonoscopy was required for all enrolled patients at final study visit in STEPS-2 (Month 24) and STEPS-3 (Month 36) or at the early termination visit for each of the extension studies. The study protocol did not prevent surveillance colonoscopies being performed, if needed; collectively these post-baseline procedures are referred to as surveillance/end-of-study colonoscopies. No colonoscopy was scheduled at the final study visit in STEPS. Information regarding polyps was collected via patient electronic case report forms. Because the nature of this analysis was to report individual colonoscopy data, only descriptive statistics are provided.

Results

A summary of the colonoscopy visits and results for each individual STEPS study can be found in **Supplementary Tables 1–3**. Of the 98 patients (mean [SD] age 50.3 [14.02] years; women 53.1%) in the STEPS studies enrolled population, 73 (mean age 49.8 [14.14] years; women 57.5%) received a pre-randomization baseline colonoscopy; 25 had no remnant colon (**Supplementary Table 1**). Of the 65 patients who had a colon in the STEPS-2 and STEPS-3 populations, three patients did not have a baseline colonoscopy and 50 patients (mean age 51.5 [13.31] years; women 56.0%) had a surveillance/end-of-study colonoscopy.

Polyps were reported in nine of 73 patients from the baseline colonoscopy (**Table 1**). Five of the nine patients had one polyp each and the remaining four patients had two or more polyps. In these patients, the duration of parenteral support, an indirect measure of SBS–IF disease duration,

ranged from one to ≥24 years. All baseline polyps detected were removed before randomization and initiation of dosing (no histology examination was required by the protocol).

Table 2 provides the detailed data for the colon polyps reported in nine (mean age 49.6 [8.80] years; women 77.8%; 193.7 [52.24] per 100 patient-years) of 50 patients who underwent surveillance/end-of-study colonoscopy. In these nine patients, polyps were detected in three patients who had polyps removed at the baseline colonoscopy (n=2) or during the 24-month STEPS-2 colonoscopy (n=1). The polyps in these three patients were located in colon/rectum (baseline) and transverse colon/ascending colon/cecum (surveillance/end-of-study) in patient No. 3, in rectum (baseline) and colorectal (surveillance/end-of-study) in patient No. 6, and colon (STEPS-2) and colon (surveillance/end-of-study) in patient No. 1. The duration of teduglutide exposure at the time of polyp discovery in the nine patients ranged from eight to 36 months. Histological analyses in seven patients reported no evidence of malignancy; various adenomas were reported in 5 patients (**Table 2**).

A duodenal polyp (no histology available) reported from a gastroscopy in a 64-year-old man with a history of smoking/asbestos exposure during investigation for a non–small cell lung cancer (STEPS-2; the duration of teduglutide exposure at polyp detection was 3 months following completion in STEPS where placebo was received) is not included in this analysis .

Discussion

In average risk adults (ie, no history of adenomatous polyps or colorectal cancer), the American Cancer Society (ACS) recommends screening as early as 45 years of age.[6] An analysis of 9100 colonoscopies from a population-based US registry cohort (mean age, 60 years), comprising 68% screening and 32% surveillance colonoscopies reported adenoma rates of 25% and 37%, respectively.[7] In patients who had no polyp detected at a baseline screening colonoscopy but had a second surveillance colonoscopy within 5.5 years the rate of adenoma was 16%-41%.[8]

In the STEPS clinical trial series, polyps were detected during the screening baseline colonoscopy in 12% (9/73) of patients, aged 39 to 75 years, who had SBS–IF. Among the patients who received long-term teduglutide and had colonoscopies during or at the end of the study, polyps were detected in 18% (9/50) of patients. This 24- and 36-month colonoscopy data could be considered a short-term 'surveillance' colonoscopy from a second protocol-driven, not risk-driven, endoscopy. Collectively in this post hoc analysis, the reported polyp detection rate for a SBS–IF population is at the low range of the rates reported in the literature for the general population.[7,8] Variations in patient demographics and baseline characteristics may account for the observed differences in rates of polyp detection. No histological information is available for the nine patients who had polyps before receiving any study treatment. Of the seven histology analyses performed in patients who received long-term teduglutide, there was no evidence of malignancy.

This post hoc analysis has a number of limitations. Although this analysis used all available colonoscopy data collected, the STEPS study program was not designed to investigate polyp formation in detail. In particular, the study design permitted a comparison between teduglutide and placebo only for the first 24 weeks of the observation period; thereafter, all patients received teduglutide for up to two years. Furthermore, the protocol was not designed to assess baseline polyp characteristics or risk factors for the development of polyps or colorectal cancer. The conclusions are, therefore, constrained by the small population size, the descriptive nature of the findings, and the limited, structured data-reporting requirements for the colonoscopy and histology procedures. We cannot rule out the possibility that polyps identified during the follow-up colonoscopy did not develop de novo between procedures, but rather were undetected during the baseline colonoscopy. We did not include data from other clinical studies, noted in some regional prescribing information documents[1], that used higher doses than the approved 0.05/mg/day teduglutide (2 cases) or included intestinal polyps (2 cases). Overall, these colonoscopy results support the recommendation in the teduglutide prescribing information

regarding colonoscopy for monitoring potential polyp development.[1,2] A polyp detection rate of 12% supports baseline colonoscopy before starting teduglutide. Moreover, careful screening at the baseline is critical to detect cancers that would otherwise preclude teduglutide therapy and for the detection and removal of polyps that might be at risk of progression during treatment. This would also minimize the risk of undetected polyps, which, if detected at the recommended 1–2 year colonoscopy, would necessitate earlier or more frequent surveillance. Most patients (>70% with no polyps at baseline or follow up colonoscopy) could then be monitored every 5 years thereafter. An ongoing global, observational SBS registry (NCT01990040; EUPAS7973) is designed to provide more detailed information on the development of colon polyps in patients with SBS-IF. Newer mechanical endoscopic devices have markedly improved detection of adenomas and polyps colonoscopy.[9] These novel diagnostics such as magnifying chromoendoscopy and magnifying narrow-band imaging, as well as histological and molecular characterization, should be considered for the evaluation of colorectal adenomas in the screening and surveillance of patients treated with teduglutide.

Conclusion

These limited data provide additional information about the risk of polyp formation in patients with SBS–IF and in patients who were treated with teduglutide. They support the recommendations for a baseline, pre-treatment colonoscopy and subsequent surveillance colonoscopies in the teduglutide regulatory prescribing labels which should be considered in conjunction with local guidelines and policies for colorectal cancer screening in average risk and high risk individuals.

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Statement of Authorship

All authors contributed to the conception of the work, analysis, or interpretation of the data and drafting or revising the manuscript, gave final approval to submit, and accept accountability for all aspects of the work. Authors had full access to the data in the analysis.

Conflict of Interest Statement

Shire is a member of the Takeda group of companies. DA has received consulting fees, honoraria, or grant/research support from and served as an advisory board member or study investigator for NPS Pharmaceuticals, Inc., Shire, AbbVie, Janssen, and Takeda. AF has received consulting fees, honoraria, and grant/research support from and served as an advisory board member and study investigator for NPS Pharmaceuticals, Inc. PBJ has served as a study investigator for NPS Pharmaceuticals, Inc., and has received consulting fees or honoraria from and served on an advisory committee or speakers bureau for Shire and Zealand Pharmaceuticals. H-ML and PN are employees of Shire. DLS has served as a study investigator for NPS Pharmaceuticals, Inc., and as a consultant for Shire and Zealand Pharmaceuticals.

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Table 1. Characteristics of patients with polyps reported at pre-randomization baseline colonoscopy[a]

Sex	Age at Screening, Years	Duration of Parenteral Support at Screening, Years	Etiology of SBS	Estimated Percent of Colon Remaining	Polyp Size	Location (Number of Polyps)
F	58	1.8	Vascular disease (embolism of superior mesenteric artery)	60	Not reported	Colon (×1)
F	45	1.9	Vascular disease (venous mesenteric infarction)	70	Not reported	Colon (×1)
M	46	5.9	Vascular disease (mesenteric infarction)	90	Not reported	Colon (×1)
M	68	7.0	Vascular disease (embolism of mesenteric artery)	100	Not reported	Colon and rectum (multiple)

F	75	5.8	Vascular disease (occlusion of superior mesenteric artery)	50	5 mm	Rectum (×1)
F	47	1.0	Vascular disease (thrombosis of mesenteric artery)	100	4 mm	Colon (×1)
					1–2 mm	Rectum (multiple)
M	39	1.7	Other (volvulus)	30	Not reported	Large intestine (multiple)
F	49	24.7	Other (injury)	100	Not reported	Rectum (×2)
F	43	1.1	Other (small bowel infarction)	100	Not reported	Not reported (×1)

Abbreviations: F, female; M, male; SBS, short bowel syndrome.

[a]No histopathology data are available.

Table 2. Characteristics of patients with polyps reported at surveillance/end-of-study colonoscopy

Pt	Sex / Age at Screening, Years	Duration of Parenteral Support at Screening, Years	Etiology of SBS	Estimated Percent of Colon Remaining	Treatment Group, STEPS/STEPS-2/STEPS-3	Polyp Detected at Baseline Colonoscopy	Duration of TED Exposure at Time of Polyp Detection, Months[a]	Location (Number of Polyps)	Size, cm	Histopathology[b]
1	F / 46	24.0	IBD (Crohn's disease)	25	PBO/TED/TED	No[c]	24	Colon (×3)	0.2–0.5	Hyperplastic polyp
							36	Colon (NR)	NR	NR
2	M / 62	3.0	Vascular disease (ischemic event)	50	PBO/TED/NA	No	24	Colon (×2)	0.3–0.5	Tubular adenomas

3	F / 47	1.0	Vascular disease (thrombosis of mesenteric artery)	Unknown	PBO/TED/NA	Yes	24	Transverse colon (×2) Ascending colon (×2) Cecum (×1)	0.3–0.7	Probable whole serrated adenomas NR NR
4[d]	F / 55	9.6[e]	Vascular disease (unknown)	50	TED/TED/NA	No	10	Rectum (×1)	NR	Inflamed polyp lesion, no neoplasm, acute proctitis with surface necrosis, acute inflammation, and prominent crypt epithelial regeneration

5	F / 41	1.9[e]	Other (injury)	75	PBO/TED/TED	No	36	Colon (×1)	NR	Not resected[f]
6	F / 49	24.7	Other (injury)	100	TED/TED/NA	Yes	8[g]	Colorectal (×3)	NR	Tubular adenoma with low-grade dysplasia , and tubulo-villous adenoma (rectum)
7	F / 61	1.2[f]	Other (strangulated intestine)	50	TED/TED/TED	No	29	Cecum (×2)	NR	Tubular adenomas
8	F / 35	4.2	Other (volvulus)	Not reported	PBO/TED/NA	No	24	Rectum (×1)	0.2	Tubular adenoma with low-grade dysplasia
9	M / 50	4.1	Other (jejunal fistula)	50	PBO/TED/NA	No	24	Not specified	NR	Not resected

Notes: [a]Exposure includes time in STEPS study, mean (SD) is 193.7 (52.24) per 100 patient-years; [b]Histology analyses in all except patients 5 and 9; [c]Polyp detected during 24-month STEPS-2 colonoscopy was removed before patient continued in STEPS-3; [d]Non-study colonoscopy performed

as part of workup for diverticulitis; [e]PS-independent by the end of study (all during STEPS-2); [f]tubular adenoma reported as colonoscopy finding;

[g]Early termination colonoscopy (Day 57).

Abbreviations: F, female; IBD, inflammatory bowel disease; M, male; NA, not applicable; NR, not reported; PBO, placebo; SBS, short bowel syndrome; TED, teduglutide.

Supplementary material

Table S1. Baseline colonoscopy results for the STEPS clinical trial series

Group	Patients With Pre-randomization Baseline Colonoscopy[a]	Patients With Stabilization Visit Only Colonoscopy	Patients With Stabilization + Repeated Stabilization Visits Colonoscopy	Patients With Repeated Stabilization Visit Colonoscopy	Patients With Polyps at Pre-randomization Baseline Colonoscopy
Subsequently randomized to placebo (n=43)[b]	33	26	6	1	4[c]
Subsequently randomized to teduglutide (n=43)	30	24	6	0	3[d]
Subsequently received teduglutide as direct OL[e] (n=12)	10	4	4	2	2[f]

Screen failures (n=22)	14	3	8	3	0
Total (screen failures omitted[g])	73	54	16	3	9[h]

Notes: [a]Colonoscopy was not performed in 25 patients who passed the screening (no colon); [b]Treatment only relevant for STEPS study; [c]All from the stabilization visit only (Patients 1, 5, 6, and 7 from Table 1); [d]Two are from the stabilization visit only (Patients 2 and 8 from Table 1) and one is from the stabilization + repeated stabilization visits (Patient 4 from Table 1); [e]Treatment only relevant for STEPS-2 study; [f]Both are from the stabilization + repeated stabilization visits (Patients 3 and 9 from Table 1); [g]Screen failures were not used because they were not part of the enrolled population; [h]Represents the nine patients shown in Table 1.

Abbreviations: OL, open-label.

Table S2. Month 24 or early termination colonoscopy results for the STEPS-2 population

Group	Number of Patients With End of Study (Month 24 or Early Termination) Colonoscopy[a]	Number of Patients With Polyps by Study Period			Total Number of Patients With Polyps at End of Study
		Baseline Only	Baseline and End of Study	End of Study Only	
Placebo (n=36)[b]	22	0	1[c]	4[d]	5
Teduglutide (n=36)	22	0	1[e]	2[f]	3
Direct OL (n=11)[g]	4	0	0	0	0
Total	48	0	2	6	8[h]

Notes: [a]Colonoscopy was not performed in 35 patients (placebo [n=14]: seven no colon, four patients refused, two patients not stable, one visit not done; teduglutide [n=14]: nine no colon, two patients refused, one visit not done, one poor prep, one examination not indicated; direct OL [n=7]: three patients visit not done, two patients refused, two patients had no colon); [b]Treatment only relevant for STEPS study; [c]Refers to Patient 3 in Table 2; [d]Refers to Patients 1, 2, 8, and 9 in Table 2; [e]Refers to Patient 6 in Table 2; [f]Refers to Patients 4 and 7 in Table 2; [g]Treatment only relevant for STEPS-2 study; [h]Represents eight of the nine patients in Table 2 (ie, Patient 5 occurrence was reported in STEPS-3).
Abbreviations: OL, open-label.

Table S3. Month 12 or early termination colonoscopy results for the STEPS-3 population

Group	Number Of Patients With End of Study (Month 12 or Early Termination) Colonoscopy[a]	Number of Patients With Surveillance (Unscheduled In-Study Visit) Colonoscopy	Number of Patients With Polyps by Study Period				Number of Patients With Polyps at End of Study
			Baseline Only	Baseline and End of Study	First Study Visit (ie, End of STEPS-2 Colonoscopy)	End of Study Only	
Placebo (n=6)[b]	4	0	0	0	1[c]	1[d]	2[e]
Teduglutide (n=5)	0	2	0	0	1[f]	0	0
Direct OL (n=3)[g]	0	1	0	0	0	0	0
Total	4[h]	3[h]	0	0	2	1[d]	2[d]

Total unique in STEPS-3			1[d]	1[i]

Notes: [a]Colonoscopy was not performed in 10 patients (placebo [n=2]: one in-study ileoscopy performed, one patient refused; teduglutide [n=5]: two in-study unscheduled visit colonoscopies, one no reason given, one patient refused, one in-study ileoscopy performed; direct OL [n=3]: one no colon, one in-study unscheduled visit colonoscopy, one patient refused); [b]Treatment only relevant for STEPS study; [c]1 patient with polyp from the first study visit (ie, last STEPS-2 visit) who had a recurrence of polyp in final STEPS-3 visit (Patient 1 from Table 2); [d]1 patient from the final STEPS-3 visit (Patient 5 from Table 2); [e]1 patient with polyp from the first study visit (ie, last STEPS-2 visit) + recurrence of polyp in final STEPS-3 visit (Patient 1 from Table 2) and 1 patient from the final STEPS-3 visit (Patient 5 from Table 2); [f]Patient from the first study visit only (ie, last STEPS-2 visit; Patient 7 from Table 2); [g]Treatment only relevant for STEPS-2 study; [h]Collectively, the seven are unique procedures within the STEPS-3 study; [i]Represents one of the nine patients in Table 2.

Abbreviations: OL, open-label.