Clinical Nutrition xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Short Communication

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

David Armstrong [a, *], Alastair Forbes [b], Palle B. Jeppesen [c], Hak-Myung Lee [d], Peter Nagy [e], Douglas L. Seidner [f]

[a] Division of Gastroenterology & Farncombe Family Digestive Health Research Institute, HSC-3V3, McMaster University, 1280 Main Street West, Hamilton, ON L8S 4K1, Canada
[b] Norwich Medical School, University of East Anglia, 2.12 Bob Champion Research & Education Bldg, Norwich, England, UK
[c] Department of Medical Gastroenterology, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark
[d] Biostatistics & Statistical Programming, Shire Human Genetics Therapies, Inc. (a Member of the Takeda Group of Companies), 300 Shire Way, Lexington, MA 02421, USA
[e] Global Clinical Development, Shire International GmbH (a Member of the Takeda Group of Companies), Zahlerweg 10, 6301 Zug, Switzerland
[f] Division of Gastroenterology, Hepatology, and Nutrition, Department of Medicine, Vanderbilt University Medical Center, 1211, 21st Avenue South, Ste 514 MAB, Nashville, TN, USA

ARTICLE INFO

Article history:
Received 27 March 2019
Accepted 19 August 2019

Keywords:
Clinical
Colon
Adenoma
Polyp
Risk
Surveillance

SUMMARY

Background & aims: Teduglutide, promotes intestinal growth and is approved for the treatment of short bowel syndrome and intestinal failure (SBS-IF) [GATTEX® (teduglutide). Full prescribing information. Shire-NPS Pharmaceuticals, Inc., Lexington, MA, USA, 2019; Revestive® (teduglutide). Full prescribing information. Shire Pharmaceuticals Ireland Limited, Dublin, Ireland, 2019.]. Based on the pharmacologic activity and preclinical findings, teduglutide can potentially induce proliferative colonic mucosal changes. 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) post-exposure procedures.

Results: In the STEPS studies, 73 patients treated with teduglutide had a baseline colonoscopy. No post-exposure colonoscopy was scheduled in STEPS. In STEPS-2/3, 50 of 65 patients with remnant colon (77%) underwent a protocol-mandated post-exposure colonoscopy. Colon polyps were reported at baseline in 12% (9/73) of patients and post-exposure in 18% (9/50) of patients. Two had polyps both at baseline and post-exposure. On histology, available for seven patients, 5 had adenomas (1 serrated, 4 tubular) and none had malignancy or high-grade dysplasia.

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 patients with SBS-IF and the most appropriate colon polyp surveillance strategies.

Abbreviations: IBD, inflammatory bowel disease; NA, not applicable; NR, not reported; PBO, placebo; SBS, short bowel syndrome; SBS-IF, short bowel syndrome and intestinal failure; STEPS, study of teduglutide effectiveness in parenteral nutrition-dependent short bowel syndrome subjects; TED, teduglutide.

* Corresponding author. Division of Gastroenterology & Farncombe Family Digestive Health Research Institute, HSC-3V3, McMaster University, 1280 Main Street West, Hamilton, ON L8S 4K1, Canada. Fax: +1 905 521 4958.
E-mail address: armstro@mcmaster.ca (D. Armstrong).

https://doi.org/10.1016/j.clnu.2019.08.020

Please cite this article as: Armstrong D et al., Colon polyps in patients with short bowel syndrome before and after teduglutide: Post hoc analysis of the STEPS study series, Clinical Nutrition, https://doi.org/10.1016/j.clnu.2019.08.020

1. Introduction

Teduglutide, an analog 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 pharmacologic activity and preclinical findings of this trophic hormone, the potential for hyperplastic changes was taken into consideration by regulatory agencies at the time of indication approval [1,2]. Consequently, the prescribing information and product monographs propose close colonoscopic surveillance. Namely, patients should have a colonoscopy with removal of polyps before the initiation of treatment with teduglutide and follow-up colonoscopies during treatment [1,2]. However, there are limited data on the development or progression of polyps in patients receiving teduglutide. The present study is not powered to challenge current surveillance recommendations, but this brief communication does provide additional, albeit limited post hoc, data regarding the baseline prevalence and incidence of potentially malignant or pre-malignant lesions in patients taking teduglutide. The data are derived from the three completed adult studies in the 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.

2. 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 eligible to participate in STEPS had short bowel syndrome and intestinal failure (SBS-IF), were parenteral support dependent for ≥12 months, and required parenteral support ≥3 times weekly. 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 in this post hoc analysis received teduglutide. 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 except those who had a normal colonoscopy within six months of their screening visit. The colonoscopy was performed at the end of the parenteral support stabilization period (baseline study visit) and before randomization to rule out malignant and high-grade dysplastic lesions. 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 the extension studies. The study protocol did not preclude surveillance colonoscopies, if needed; collectively these post-baseline procedures are referred to as post-exposure colonoscopies. Information regarding polyps was collected via patient electronic case report forms; a histology report for any resected lesions was not required. Because the nature of this analysis was to report individual colonoscopy data, only descriptive statistics are provided.

3. Results

In the STEPS studies, 73 patients (mean [SD] age 49.8 [14.14] years; women 57.5%) had a remnant colon and received a pre-randomization baseline colonoscopy (Supplementary Table 1). No post-exposure protocol colonoscopy was scheduled in the STEPS study. In the STEPS-2 and STEPS-3 populations, of the 65 patients who had a colon 50 patients (77%; mean age 51.5 [13.31] years; women 56.0%) had a protocol-mandated post-exposure colonoscopy. A summary of the colonoscopy visits and results for each individual STEPS study can be found in Supplementary Tables 1–3.

Polyps were reported in nine of 73 patients who underwent 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.

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 post-exposure 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 (post-exposure) in patient No. 6, in rectum (baseline) and colorectal (post-exposure) in patient No. 8, and colon (STEPS-2) and colon (post-exposure) in patient No. 10. 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 or high-grade dysplasia; various adenomas were reported in 5 patients (Table 2).

A duodenal polyp (no histology available), detected at gastroscopy in a 64-year-old man, is not included in the analysis; this patient had a history of smoking/asbestos exposure and was being investigated 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).

4. Discussion

In average risk adults (ie, no history of adenomatous polyps or colorectal cancer), the American Cancer Society 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 with SBS-IF, aged 39–75 years. Among the patients who received long-term teduglutide and had post-exposure colonoscopies, polyps were detected in 18% (9/50) of patients. This 24- and 36-month colonoscopy data could be considered a short-term second protocol-driven, not risk-driven, 'surveillance' colonoscopy. 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

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

Patient number	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)
1	F	58	1.8	Vascular disease (embolism of superior mesenteric artery)	60	Not reported	Colon (×1)
2	F	45	1.9	Vascular disease (venous mesenteric infarction)	70	Not reported	Colon (×1)
3	M	46	5.9	Vascular disease (mesenteric infarction)	90	Not reported	Colon (×1)
4	M	68	7.0	Vascular disease (embolism of mesenteric artery)	100	Not reported	Colon and rectum (multiple)
5	F	75	5.8	Vascular disease (occlusion of superior mesenteric artery)	50	5 mm	Rectum (×1)
6[b]	F	47	1.0	Vascular disease (thrombosis of mesenteric artery)	100	4 mm 1–2 mm	Colon (×1) Rectum (multiple)
7	M	39	1.7	Other (volvulus)	30	Not reported	Large intestine (multiple)
8[b]	F	49	24.7	Other (injury)	100	Not reported	Rectum (×2)
9	F	43	1.1	Other (small bowel infarction)	100	Not reported	Not reported (×1)

F, female; M, male; SBS, short bowel syndrome.
[a] No histopathology data are available.
[b] Patient also had polyps reported at a post-exposure colonoscopy.

patients who received long-term teduglutide, there was no evidence of malignancy or high-grade dysplasia.

This post hoc analysis has some limitations. Although this analysis used all available colonoscopy data collected, the STEPS study program was not designed to investigate polyp formation in detail. Particularly, the study design permitted a comparison between teduglutide and placebo for the first 24 weeks; thereafter, all patients received teduglutide for up to two years. Furthermore, the

Table 2
Characteristics of patients with polyps reported at post-exposure colonoscopy.

Patient number	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]
6[d]	F/47	1.0	Vascular disease (thrombosis of mesenteric artery)	100	PBO/TED/NA	Yes	24	Transverse colon (×2) Ascending colon (×2) Cecum (×1)	0.3–0.7	Probable whole serrated adenomas NR NR
8[d]	F/49	24.7	Other (injury)	100	TED/TED/NA	Yes	8[h]	Colorectal (×3)	NR	Tubular adenoma with low-grade dysplasia, and tubulo-villous adenoma (rectum)
10	F/46	24.0	IBD (Crohn's disease)	25	PBO/TED/TED	No[c]	24 36	Colon (×3) Colon (NR)	0.2–0.5 NR	Hyperplastic polyp NR
11	M/62	3.0	Vascular disease (ischemic event)	50	PBO/TED/NA	No	24	Colon (×2)	0.3–0.5	Tubular adenomas
12[e]	F/55	9.6[f]	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
13	F/41	1.9[f]	Other (injury)	75	PBO/TED/TED	No	36	Colon (×1)	NR	Not resected[g]
14	F/61	1.2[g]	Other (strangulated intestine)	50	TED/TED/TED	No	29	Cecum (×2)	NR	Tubular adenomas
15	F/35	4.2	Other (volvulus)	Not reported	PBO/TED/NA	No	24	Rectum (×1)	0.2	Tubular adenoma with low-grade dysplasia
16	M/50	4.1	Other (jejunal fistula)	50	PBO/TED/NA	No	24	Not specified	NR	Not resected

F, female; IBD, inflammatory bowel disease; M, male; NA, not applicable; NR, not reported; PBO, placebo; SBS, short bowel syndrome; TED, teduglutide.
[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] Patient also had polyps reported at a pre-randomization baseline colonoscopy.
[e] Non-study colonoscopy performed as part of workup for diverticulitis.
[f] PS-independent by the end of study (all during STEPS-2).
[g] Tubular adenoma reported as colonoscopy finding.
[h] Early termination colonoscopy (Day 57).

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protocol was not designed to capture baseline polyp characteristics, risk factors for the development of polyps or colorectal cancer, or prior colonoscopies in patients >50 years of age. The conclusions are, therefore, constrained by the small population size, the descriptive nature of the findings, and the limited data-reporting requirements for the colonoscopy and histology. It is possible 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 colonoscopic surveillance [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 and may lead to revision of the current regulatory guidance on surveillance colonoscopy. Newer mechanical endoscopic devices such as magnifying chromoendoscopy and magnifying narrow-band imaging have markedly improved detection of adenomas and polyps [9]. It is possible that these novel diagnostics along with histological, molecular, and stool-based techniques may be adopted, after appropriate validation, for screening and surveillance of patients treated with teduglutide.

5. Conclusion

These data provide some additional information about the risk of polyp formation in patients with SBS-IF and in patients 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.

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.

Conflicts of interest

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.

Role of the funding source

Shire is a member of the Takeda group of companies. The funding for this post hoc analysis was provided by Shire International GmbH, Zug, Switzerland. Under the direction of the authors and funded by Shire, editorial support and writing assistance by Maryann T. Travaglini, PharmD, was provided by Complete Healthcare Communications, LLC, a CHC Group company (North Wales, PA, USA).

Acknowledgments

The authors are grateful to all participating patients and their families and the clinical investigators and staff at all participating centers for their contributions to the entire STEPS clinical trial program. Gratitude is also extended to Clément Olivier, MD, of Shire International GmbH, Zug, Switzerland, a member of the Takeda group of companies, for his support during the initiation of this post hoc analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2019.08.020.

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