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Enteral Autonomy and Days Off Parenteral Support With Teduglutide Treatment for Short Bowel Syndrome in the STEPS Trials

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Abstract

Background: Teduglutide response, in terms of parenteral support (PS) volume reduction, is associated with specific disease characteristics among adults with short bowel syndrome–associated intestinal failure (SBS-IF). Whether these associations apply to PS weaning with teduglutide is unknown. *Methods:* Adults with SBS-IF treated with teduglutide in the phase III STEPS study and open-label extensions STEPS-2 and STEPS-3 were included in the analysis. Patients required PS ≥ 3 times weekly for ≥ 12 months at enrollment. The study population was stratified 3 times to create 3 distinct analysis populations based on bowel anatomy, etiology, and baseline PS volume. Outcomes included characteristics of patients who achieved PS independence and total and percentage of patients who had ≥ 1, ≥ 2, and ≥ 3 d/wk off PS at the end of STEPS, STEPS-2, and STEPS-3. *Results:* Eight of 39 patients who received teduglutide in STEPS obtained PS independence during the STEPS study series. Patients required > 6 months of teduglutide treatment before enteral autonomy was achieved, regardless of underlying disease characteristics. Patients who attained PS independence and greater numbers of days per week off PS tended to have lower baseline PS volumes and noninflammatory bowel disease (non-IBD) etiology. Patients with ≥ 50% colon-in-continuity showed a trend for achieving greater numbers of days per week off PS. *Conclusion:* Although this analysis was limited by low patient numbers, results suggest that SBS-IF characteristics of lower baseline PS volume and non-IBD etiology were associated with PS reduction benefits with teduglutide in terms of days off per week and enteral autonomy. (*JPEN J Parenter Enteral Nutr.* 2020;44:697–702)

Keywords

gastroenterology; independence; intestinal failure; parenteral nutrition; short bowel syndrome; weaning

Clinical Relevancy Statement

In the STEPS randomized controlled trial and its open-label extensions (STEPS-2 and STEPS-3), teduglutide reduced parenteral support (PS) requirements in patients with intestinal failure associated with short bowel syndrome (SBS-IF). In this post hoc analysis of the STEPS study series, patients who achieved PS independence and greater

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numbers of days off PS per week tended to have lower baseline PS volume requirements and noninflammatory bowel disease as the cause of SBS-IF. Additionally, patients with ≥50% colon remaining showed a trend for greater number of days per week off PS. This study helps clarify disease characteristics associated with teduglutide effects.

Introduction

The clinical features of intestinal failure associated with short bowel syndrome (SBS-IF), including parenteral support (PS; parenteral nutrition, and/or intravenous fluids) volume needs, vary according to the extent and cause of intestinal resection and residual anatomy.[1-3] Teduglutide, a glucagon-like peptide (GLP)-2 analogue, is approved in the United States and Europe for the treatment of patients aged ≥1 year with SBS-IF,[4,5] and has been shown to improve intestinal absorption and reduce PS requirements in patients with SBS-IF.[6-8] In the phase III, 24-week, placebo-controlled STEPS study (NCT00798967; EudraCT, 2008-006193-15), individual patient response to teduglutide in terms of PS volume reduction was variable, with PS volume change from baseline at week 24 ranging from –1993 to 329 mL/d.[2]

Recently, Jeppesen et al evaluated clinical and disease characteristics associated with PS volume reduction with teduglutide treatment in patients from the STEPS study.[2] Among all patients treated with teduglutide, absolute baseline PS volume requirements were significantly correlated with absolute PS volume reduction; no correlation was seen among placebo-treated patients. Compared with other remnant bowel anatomies, patients with a jejunostomy or ileostomy and no colon remaining had the highest PS volumes at baseline and experienced the greatest PS volume reductions with teduglutide. Compared with vascular or other causes of SBS-IF, patients with inflammatory bowel disease (IBD) as a cause of SBS-IF had higher PS volume requirements at baseline and experienced the greatest PS volume reductions with teduglutide. Beyond PS volume reductions, 2 unanswered questions were the extent that these distinct disease characteristics may contribute to the effects of teduglutide in terms of achieving PS independence and days per week off PS. To answer those clinically relevant questions for physicians, post hoc analysis of data from the 3 studies in the STEPS series, STEPS and the 24-month STEPS-2 (NCT00930644; EudraCT, 2009-011679-65)[9] and 12-month STEPS-3 (NCT01560403)[10] extension studies, assessed for the first time if any pattern existed.

Methods

Study Design and Patients

This post hoc analysis included data from teduglutide-treated patients enrolled in the STEPS study, a 24-week, phase III, multicenter, multinational, randomized, placebo-controlled trial,[7] and STEPS-2[9] and STEPS-3,[10] the STEPS extension studies. In STEPS, patients were randomized 1:1 to subcutaneous teduglutide (0.05 mg/kg/d) or placebo. STEPS-2 was a 2-year, open-label, multicenter, multinational extension.[9] STEPS-3 was a 1-year, open-label extension of STEPS-2 conducted in the United States.[10] All patients in STEPS-2 and STEPS-3 received subcutaneous teduglutide (0.05 mg/kg/d). All studies were conducted in accordance with the Declaration of Helsinki, the International Conference on the Harmonization Guidelines, and Good Clinical Practice. All study protocols were approved by local institutional review boards or medical ethics committees. Full study details have been published previously.[7,9,10]

STEPS enrolled adult patients with SBS who required PS ≥3 times weekly for ≥12 continuous months. Upon completion of STEPS, patients could choose to enroll in STEPS-2 and subsequently STEPS-3. Total treatment time for patients who received teduglutide in STEPS and completed STEPS-2 and STEPS-3 was 42 months.

PS Optimization and Adjustments

Before randomization in STEPS, patients underwent a PS optimization period as needed, in which PS was adjusted to achieve a target urine output of 1–2 L/d. In STEPS, PS reductions of 10%–30% of baseline volume were permitted at a 2-week interval to a 4-week interval if clinical status was stable and 48-hour urine output increased by ≥10% over baseline. During STEPS-2 and STEPS-3, PS adjustments were made according to the same protocol but less frequently (at a 2-week interval to a 12-week interval in STEPS-2 and 12-week intervals in STEPS-3).

Analysis Population

The analysis population included 39 patients who received teduglutide and completed the STEPS study, including those who continued to receive teduglutide in STEPS-2 and STEPS-3; 1 patient randomized to teduglutide in STEPS was excluded because the patient discontinued before the first dose and did not undergo any study assessments. The study population was stratified 3 times to create 3 distinct analysis populations based on the following:

1. Bowel anatomy subgroups: (a) patients with 0% colon remaining, stoma present, and no colon-in-continuity; (b) patients with ≥50% colon remaining, no stoma present, and colon-in-continuity; and (c) patients with <50% colon remaining or with colostomy
2. Etiology subgroups: (a) SBS-IBD (patients with IBD as an underlying cause of SBS-IF), (b) SBS-Vasc (patients with vascular disease as underlying cause

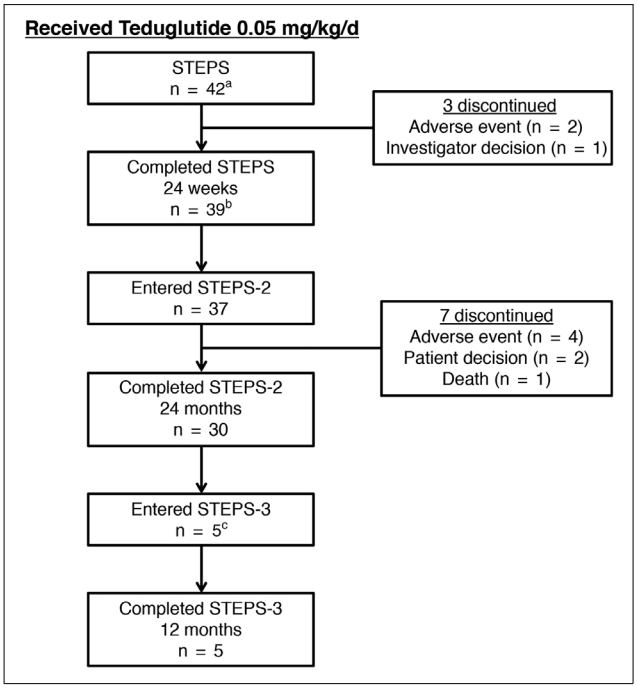

Figure 1. Flow diagram of patients in the STEPS study series. [a]1 additional patient randomized to teduglutide in STEPS was excluded because the patient discontinued before the first dose and did not undergo any study assessments. [b]Population included in the present analysis. [c]STEPS-3 was conducted at sites in the United States only; patients from other countries were not eligible to participate.

of SBS-IF), and (c) other (patients with other underlying causes of SBS-IF)

3. Baseline PS volume subgroups: (a) ≤ 9 L/wk PS at baseline, (b) > 9–18 L/wk PS at baseline, and (c) > 18 L/wk PS at baseline

Outcomes included the characteristics of patients treated with teduglutide who achieved complete PS independence and the total and percentage of patients who had ≥ 1, ≥ 2, and ≥ 3 d/wk off PS at the end of STEPS, STEPS-2, and STEPS-3 for each of the 3 sets of patient stratifications. Baseline was defined as the start of teduglutide treatment in STEPS.

Statistical Analysis

Analysis was performed using descriptive statistics. No between-group comparisons were performed because of the small patient numbers.

Results

Forty-two patients received teduglutide in the placebo-controlled STEPS study (Figure 1). Three patients discontinued STEPS because of adverse events (AEs; n = 2) or investigator decision (n = 1); 39 patients completed the study and are included in this analysis. Thirty-seven of the 39 teduglutide-treated patients who completed STEPS chose to enroll in STEPS-2. Seven of these patients discontinued STEPS-2 before study completion because of AEs (n = 4), patient decision (n = 2), or patient death (n = 1). Five US-based patients who received teduglutide in STEPS and completed STEPS-2 elected to enroll in the US-based STEPS-3 extension study; all 5 completed STEPS-3.

During the STEPS study series, 8 patients treated with teduglutide achieved enteral autonomy by weaning off PS (ie, PS stoppage was not due to AEs and PS was not resumed during the studies) (Table 1). None of the patients became PS independent during the initial 24-week STEPS trial; all 8 patients weaned off during STEPS-2, and 1 patient who continued into STEPS-3 maintained PS independence through the end of STEPS-3. No other patient enrolled in STEPS-3 who received teduglutide in STEPS obtained enteral autonomy. The characteristics of patients who obtained PS independence in the STEPS study series are detailed in Table 1. Six of 8 patients who achieved enteral autonomy had a baseline PS volume of ≤9 L/wk. The bowel anatomy and etiology classifications varied among the 8 patients who weaned off PS.

Table 2 reports the post hoc analysis of the number of days per week off PS for the patients who received teduglutide during the STEPS study series when stratified by the 3 distinct subgroups. A greater percentage of patients in the lowest baseline PS volume subgroups had higher numbers of days per week off PS at the end of STEPS and STEPS-2 than the other 2 PS volume subgroups. The patient subgroup with ≥ 50% colon remaining/no stoma/colon-in-continuity showed a trend for more patients having the higher number of days off PS compared with patients with 0% colon remaining/stoma/no colon-in-continuity and patients with other bowel anatomies. When patients were stratified by disease etiology, patients with a vascular or other acute cause of SBS-IF showed a possible trend for increased numbers of days off PS at the end of STEPS and STEPS-2 compared with patients with IBD as a cause of SBS-IF.

Discussion

The findings of this post hoc analysis support the need for individualized management of adults with SBS-IF who are receiving teduglutide.[2,11,12] Patients who obtained PS independence had a range of characteristics with regard to age, bowel anatomy, and etiology of SBS-IF; however, the underlying cause of SBS-IF was non-IBD related in half of the cases, and most patients had lower PS volumes at baseline. Although not an absolute cutoff, patients who achieved enteral autonomy in these clinical studies had baseline PS volumes of ≤ 14 L/wk. Enteral autonomy in all 8 patients was achieved after the initial 6-month teduglutide

Table 1. Characteristics of Teduglutide-Treated Patients Who Obtained Enteral Autonomy in the STEPS Study Series.[a]

Study Enrollment When Weaned From PS	Age, years; Sex	Duration of PS Dependency at Start of TED, years	PS Volume at Baseline, L/wk[b]	PS Infusion Requirement at Start of TED, d/wk[c]	Days per Week Off PS at End of STEPS/ STEPS-2/ STEPS-3	Weeks on TED at PS Weaning	Bowel Anatomy Subgroup	Etiology Subgroup
STEPS-2	69; F	5	3.52	3	4.5/7/NA	101	≥50% of colon/no stoma/colon-in-continuity	SBS-Vasc
STEPS-2	63; M	16	13.38	4.5	3.5/7/NA	115	<50% of colon or with colostomy	SBS-Vasc
STEPS-2	46; M	6	8.87	4	3.5/7/NA	89	0% colon/stoma/no colon-in-continuity	SBS-IBD
STEPS-2	50; M	1	13	6	5/7/NA	32	0% colon/stoma/no colon-in-continuity	SBS-IBD
STEPS-2	46; F	1	3.50	3.5	6/7/NA	28	0% colon/stoma/no colon-in-continuity	SBS-IBD
STEPS-2 (continued into and maintained PS independence through the end of STEPS-3)	61; F	1	4.05	4.5	4/7/7	101	≥50% of colon/no stoma/colon-in-continuity	Other (strangulated small intestine)
STEPS-2	66; F	7	4.35	3	5/7/NA	89	<50% of colon or with colostomy	Other (radiation enteritis)
STEPS-2	39; M	13	6.75	3	5/7/NA	75	≥50% of colon/no stoma/colon-in-continuity	Other (injury)

F, female; IBD, inflammatory bowel disease; M, male; NA, not applicable; PS, parenteral support (parenteral nutrition and/or intravenous fluids); SBS, short bowel syndrome; TED, teduglutide; Vasc, vascular disease.

[a] Among patients who received teduglutide in STEPS.

[b] PS volume subgroups: patients were categorized by ≤9, >9–18, or >18 L/wk.

[c] PS requirements at the start of teduglutide are based on the 14 days before the baseline visit.

Table 2. Days Per Week Off PS During the STEPS Study Series by Patient Stratification Subgroups.

Absolute Days off PS per Week at End of Study, n (%)	PS volume subgroups		
	≤9 L/wk	>9–18 L/wk	>18 L/wk
STEPS	n = 13	n = 19	n = 7
≥1 d/wk	12 (92.3)	15 (78.9)	1 (14.3)
≥2 d/wk	12 (92.3)	10 (52.6)	0
≥3 d/wk	11 (84.6)	8 (42.1)	0
STEPS-2	n = 9	n = 16	n = 5
≥1 d/wk	8 (88.9)	13 (81.3)	1 (20)
≥2 d/wk	8 (88.9)	12 (75)	1 (20)
≥3 d/wk	8 (88.9)	11 (68.8)	1 (20)
PS independence	6 (66.7)	2 (12.5)	0
STEPS-3	n = 2	n = 2	n = 1
≥1 d/wk	1 (50)	1 (50)	1 (100)
≥2 d/wk	1 (50)	1 (50)	1 (100)
≥3 d/wk	1 (50)	1 (50)	1 (100)
PS independence	1 (50)	0	0
	Bowel anatomy subgroups		
	0% Colon remaining/ stoma/no colon-in-continuity	≥50% Colon remaining/ no stoma/colon-in-continuity	<50% Colon or with colostomy
STEPS	n = 14	n = 18	n = 7
≥1 d/wk	7 (50)	16 (88.9)	5 (71.4)
≥2 d/wk	6 (42.9)	12 (66.7)	4 (57.1)
≥3 d/wk	5 (35.7)	10 (55.6)	4 (57.1)
STEPS-2	n = 10	n = 13	n = 7
≥1 d/wk	6 (60)	11 (84.6)	5 (71.4)
≥2 d/wk	6 (60)	11 (84.6)	4 (57.1)
≥3 d/wk	6 (60)	10 (76.9)	4 (57.1)
PS independence	3 (30)	3 (23.1)	2 (28.6)
STEPS-3	n = 2	n = 2	n = 1
≥1 d/wk	1 (50)	1 (50)	1 (100)
≥2 d/wk	1 (50)	1 (50)	1 (100)
≥3 d/wk	1 (50)	1 (50)	1 (100)
PS independence	0	1 (50)	0
	Etiology subgroups		
	SBS-IBD	SBS-Vasc	Other
STEPS	n = 9	n = 15	n = 15
≥1 d/wk	4 (44.4)	12 (80)	12 (80)
≥2 d/wk	4 (44.4)	9 (60)	9 (60)
≥3 d/wk	4 (44.4)	8 (53.3)	7 (46.7)
STEPS-2	n = 6	n = 11	n = 13
≥1 d/wk	4 (66.7)	9 (81.8)	9 (69.2)
≥2 d/wk	4 (66.7)	9 (81.8)	8 (61.5)
≥3 d/wk	4 (66.7)	8 (72.7)	8 (61.5)
PS independence	3 (50)	2 (18.2)	3 (23.1)
STEPS-3	n = 0	n = 3	n = 2
≥1 d/wk	-	2 (66.7)	1 (50)
≥2 d/wk	-	2 (66.7)	1 (50)
≥3 d/wk	-	2 (66.7)	1 (50)
PS independence	-	0	1 (50)

IBD, inflammatory bowel disease; PS, parenteral support (parenteral nutrition and/or intravenous fluids); SBS, short bowel syndrome; Vasc, vascular disease.

exposure in the STEPS study (ie, after the blinded, placebo-controlled portion of the series; range 28–115 weeks), supporting a treatment management plan that allows sufficient time for optimal outcomes with teduglutide to be achieved. One patient who obtained enteral autonomy in STEPS-2 maintained PS independence through the 12-month STEPS-3 study, demonstrating long-term efficacy.

Beyond the PS independence outcome, this analysis provides additional information about the patient heterogeneity for teduglutide effect on the number of days per week off PS. A greater percentage of adult patients with low PS volume at baseline, vascular or other non-IBD causes of SBS-IF, and colon-in-continuity (≥ 50% remaining) tended to have higher numbers of days off PS. Nonetheless, it is important to note that patients in all subgroups receiving short-term or long-term teduglutide had ≥ 1 d/wk off PS.

Disease severity and resection type determine the need for PS in patients with SBS.[1] Patients with ≥50% of colon-in-continuity generally do not have large fluid/electrolyte losses but may have large losses in macronutrients.[6] In the phase II teduglutide study, which examined both fluid and energy balance, an improvement in energy absorption was the most substantial benefit associated with teduglutide treatment for these patients.[6] Considering that the algorithm used for reducing PS requirements during the STEPS clinical studies was mainly driven by changes in urine volume,[7,9,10] this may explain why this bowel anatomy subgroup, which had more patients with a higher number of days off PS at the start of the trial, needed > 6 months before achieving enteral autonomy.

This analysis was performed on a small patient sample size, particularly from the STEPS-3 study, which limits generalizations from the outcomes. Additional limitations included the more intensive schedule of potential PS adjustments in STEPS (adjustments possible from a 2-week interval to 4-week interval) as compared with STEPS-2 (2-week interval to 12-week intervals) and STEPS-3 (12-week intervals)[7,9,10] and the post hoc nature of the analysis. Because of the open-label design of the long-term extension studies, we cannot address the potential role of spontaneous adaptation[13] (vs teduglutide effect) in permitting days off PS per week and PS independence. In this analysis, an increased number of days per week off PS was associated with a bowel anatomy of ≥ 50% colon remaining/no stoma/colon-in-continuity. In previous studies reporting on the natural history of SBS, the probability of enteral autonomy was increased for patients with longer colon length or colon-in-continuity and decreased for patients with an end-jejunostomy.[13-15] Patients with colon-in-continuity may have a greater innate potential for adaptation because of the colon's role in fluid absorption and energy conservation and because L cells in the distal ileum and colon produce peptide YY, GLP-1, and GLP-2.[3,16,17] Nonetheless, patients who gained enteral autonomy in this

study had varied bowel anatomy and underlying disease characteristics. In addition, 6 of the 8 patients who weaned from PS did so after > 2 years of PS dependence, past the period in which most (but not all) of adaptive responses occur.[13,14,18] Together, these observations suggest a potential role for teduglutide in stimulating endogenous adaptation.

This post hoc analysis expands physicians' understanding of the distinct response profile for adult patients receiving teduglutide. We previously described that the greatest PS volume reductions were experienced by patients who had underlying SBS-IF characteristics that contributed to a high PS volume requirement.[2] Now we describe how alternative underlying SBS-IF characteristics of lower baseline PS volumes and a non-IBD etiology could result in a PS reduction benefit in terms of days off per week or enteral autonomy. In contrast, patients with jejunostomy and high baseline PS requirements may benefit from teduglutide through a reduction in volume output without decreasing the number of days of PS.

Data Sharing Statement

The datasets, including individual participants' data behind the results reported in this article, will be available 3 months after the submission of a request to researchers who provide a methodologically sound proposal after deidentification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization. Data requests should follow the process outlined in the Data Sharing section on Shire's website (www.shiretrials.com) and should be directed to clinicaltrialdata@shire.com. For approved requests, the researchers will be provided access to deidentified/anonymized data on a password-protected website upon Shire's receipt of a signed Data Sharing Agreement.

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Statement of Authorship

H.-M. Lee, C. Olivier, and P. B. Jeppesen contributed to the conception and design of the research. All authors contributed to the acquisition and analysis of the data. D. L. Seidner, S. M. Gabe, C. Olivier, and P. B. Jeppesen drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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