Original article

Experience with teduglutide treatment for short bowel syndrome in clinical practice

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SUMMARY

Background & aims: Teduglutide, a glucagon-like peptide 2 (GLP-2) analog, is an approved medication specific for short bowel syndrome patients with chronic intestinal failure (SBS-IF). Due to its intestinotrophic properties, it improves intestinal absorption of fluids and nutrients, which was shown to reduce the need for parenteral support in clinical trials. The present report aims to describe the experience of teduglutide's effects in routine medical care with focus on clinical and nutritional effects.
Methods: Data of adult SBS-IF patients, treated with teduglutide between Sept. 2014 and May 2017 within a structured multidisciplinary program to enhance intestinal rehabilitation, were analyzed retrospectively from a single university medical center.
Results: In total, 27 patients were treated with teduglutide. Parenteral nutrition independency was achieved in 4/19 (21%) patients analyzed, with two remaining on intravenous fluids. A clinically significant reduction of parenteral volume was observed in 15/19 patients (79%) with onset between 1 and 45 weeks. Significant parenteral support reductions were observed, ranging from about −20% in patients treated for 3 months to about −45% in patients treated for 2 years. This was accompanied by an increase in parenteral nutrition-free days. We also report on a clinically relevant and significant effect of teduglutide-mediated improvement of stool frequency and consistency. Furthermore, nutritional status subgroup analysis revealed long-term stability in body weight, albumin levels and body composition albeit parenteral support reduction. Structural effects of teduglutide treatment were observed on small intestinal mucosa with significantly increased villus height, crypt depth and plasma citrulline levels.
Conclusions: Teduglutide can be applied to anatomically and clinically heterogeneous SBS-IF patients and results in an adaptive response with variable time and effect range in routine medical care. Teduglutide-induced functional and structural changes bring on a gradual reduction of parenteral support at no cost

to body composition and suggest an improved intestinal function with compensatory effect on nutritional status.

1. Introduction

Chronic intestinal failure is a complex clinical condition caused by congenital defects, disease-associated loss of absorptive intestinal function or extensive surgical resection of the bowel resulting in short bowel syndrome (SBS) [1,2]. The resultant decrease in small intestinal surface area — which leads to inability to maintain fluid-, micro- and/or macronutrient homeostasis — is termed intestinal failure (IF) [3]. Patients with SBS suffering from IF (SBS-IF) are dependent on parenteral support (PS) with nutrients and/or fluids [4]. Based on energy and fluid/electrolyte requirements, IF can be categorized into 8 clinical subgroups as suggested by ESPEN [5], to evaluate the efficacy of an intervention [6]. SBS is clinically symptomatic with (severe) osmotic diarrhea and malabsorption, which — if left untreated — leads to severe malnutrition, dehydration and resulting life-threatening complications [4]. SBS-IF treatment generally consists of several parallel strategies to be adapted to each patient: Medical anti-secretory and anti-diarrheal treatment, nutritional therapy, surgical management and approaches to enhance intestinal adaptation [4,7,8].

The human intestinal tract reacts to extensive resection with an adaptive response, which involves mediators such as growth factors, enterohormones and nutrients [3,9–12]. The majority of adaptive processes and functional rehabilitation is thought to happen during the first post-surgical years [13–15], although late adaptation many years following resection has also been observed [15–17]. The presence of colon in continuity has been associated with a higher rate of successful weaning from PS and shorter duration of PS-dependency [13,14,16]. However, only recently the option of pharmacological enhancement of the intestinal adaptation by daily subcutaneous administration of teduglutide, an analog of endogenous glucagon like peptide-2 (GLP-2), has become available to clinical SBS-IF management [18]. GLP-2 is a meal-stimulated hormone, secreted by enteroendocrine L-cells of the small and large intestine [19–21]. In SBS-patients, GLP-2 induces proabsorptive changes, for instance prolonged gastric emptying, increased mesenteric blood flow, mucosal absorption as well as small intestinal villus hypertrophy [22,23]. Thus, administration of teduglutide in SBS-IF was shown to result in i) an increased absolute wet weight absorption and consecutive urine excretion [24] ii) an increase in small bowel villus height and crypt depth [24,25] and iii) an increase in plasma citrulline [26], an amino acid marker for enterocyte mass [27]. Two randomized controlled phase III clinical trials (one being the so called STEPS-trial which was pivotal for teduglutide approval [28]) showed under a strict parenteral weaning algorithm that teduglutide treatment resulted in significantly reduced parenteral volume requirements [25,28] while the effect on calorie supplementation has not been so clear.

Meanwhile, teduglutide has been approved for medical treatment of SBS-IF patients who are dependent on PS. It is expected to improve intestinal adaptation/rehabilitation, reduce PS requirements, and stabilize nutritional status [18], which can be monitored by bioelectrical impedance analysis (BIA) [29]. So far, publications on treatment effects of teduglutide in SBS-IF patients are limited to two controlled clinical trial programs [25,28,30,31] and their respective post hoc analyses [32,33] and one single-center experience from the U.S. [34]. Here, results from a European interdisciplinary center-based retrospective data analysis of prospectively collected observational data of patients treated within a structured program to enhance intestinal adaptation by teduglutide in benign SBS-IF are presented with focus on the nutritional and clinical effects of teduglutide in a real-life setting.

2. Subjects and methods

2.1. Patient characteristics

All adult patients with benign SBS-IF treated by an interdisciplinary team (gastroenterology, visceral surgery, nutrition care), who have received teduglutide since its approval in Germany in September 2014, were included in this observational study with retrospective data analysis. Participants of the phase III clinical teduglutide trials or patients with missing data at the first time point of follow-up data analysis were not included. Anatomic characteristics of the remnant intestinal tract were taken from surgical reports or small bowel follow through analyses. Small bowel length was described as post-duodenal remnant length, if available. Duration of chronic IF before treatment was defined as years between onset of parenteral support and first teduglutide exposure. Onset of chronic IF was considered as postsurgical time when either intermittent or continuous cyclic PS had been initiated. All analyzed patients presented clinically and nutritionally stable before teduglutide initiation and had been optimized for conventional antisecretory and antidiarrhoeal medication. Patients regularly attended our outpatient IF center and clinical symptoms, nutritional status parameters and infusion management were continuously and prospectively documented and retrospectively analyzed after up to two years on teduglutide (indicated in legends as weeks ± standard deviation, SD). Written informed consent for treatment within our unit, documentation and anonymized scientific analysis of resultant data was routinely obtained in concordance with hospital rules. PS, teduglutide and other concomitant medication were prescribed according to national and international clinical practice guidelines [4,35].

2.2. Parenteral support

Parenteral support (PS), which is defined as either fluid and electrolytes alone (intravenous fluid, IVF) or as macronutrients containing admixture (parenteral nutrition, PN), was optimized within routine medical care based on caloric and volume needs as well as clinical requirements before teduglutide treatment. Adjustment of PS during teduglutide treatment was based on changes in body weight (BW), changes in 48 h fluid intake/urine output balancing results, clinical symptoms of volume overload (edema, dyspnea), stability or improvement in bioelectrical impedance results, subjective thirst perception, physical performance and subjective patient's lifestyle requirements. PS data at baseline and weeks 12, 24, 52, 78 and 104 were defined as PS details obtained from the most current patient visit before/at indicated time point. As PS application was modified solely by our center and documentation was continuous, no standard deviation for time specification was calculated. Subjects who demonstrated reductions of ≥20% in parenteral volumes from baseline at two consecutive visits at or before week 12 were described as early responders and at weeks 24, 52 and 104 as responders [25,30,31].

2.3. Stool characteristics

Stool frequency per 48 h was regularly documented and stool consistency was classified by patients into five categories: liquid, mushy, soft blobs, firm and constipation correlating to Bristol Stool Form Scale categories 7, 6, 5, 4 to 2 & 1, respectively [36].

2.4. Bioelectrical impedance analysis

Body composition was measured with bioelectrical impedance device (Nutriguard-M, Data Input, Germany) when clinically necessary and as described elsewhere [37]. Results from routine bioelectrical impedance analysis (BIA) measurements before teduglutide treatment were used as baseline data for studying body composition changes, if a patient was in a stable physical condition. Patients who showed abnormal raw impedance data probably due to inadequate tissue hydration (no clinical manifestations visible) or measurement errors were excluded from subsequent statistical analysis of equation derived body composition parameters to avoid erroneous prediction of body compartments [38].

2.5. Blood parameters

Serum albumin and plasma citrulline were measured routinely from non-fasted patients when clinically appropriate. Albumin levels are affected by inflammatory illness [39], but inflammatory marker review of our cohort showed no evidence of acute phase response. Albumin levels were determined photometrically and citrulline levels were determined by high-pressure liquid chromatography in the central clinical chemistry laboratory. Normal reference values were 35—52 g/L for albumin and 12—55 μM for citrulline.

2.6. Intestinal mucosa structure

Small intestinal biopsies were obtained during routine endoscopy from the distal duodenum or upper jejunum, which was performed to exclude any type of upper gastrointestinal neoplasia and to obtain tissue biopsies to monitor the previously described structural effects of teduglutide on small intestinal mucosa [40]. The formalin fixed tissue samples were embedded in paraffin. After preparation of hematoxylin and eosin stained histological slides, villus height and crypt depth of the longest, well oriented villus/crypt were evaluated by the same expert pathologist blinded to teduglutide treatment using an Olympus BX50 light microscope combined with a Moticam 3 digital camera and Motic Images Plus 2.0 software. Villus height was measured from the tip of the villus to the villus crypt junction; crypt depth was defined from the valley between individual villus to the basal membrane.

2.7. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics, version 24 (SPSS GmbH, Munich, Germany). Metric values were tested for normal distribution using the Shapiro Wilk test justifying parametric statistical testing for this analysis. If normal distribution was confirmed, follow up vs. baseline values were analyzed using the Student's paired t-test. If hypothesis for normal distribution of metric values was rejected or variables were ordinal-scaled, Wilcoxon signed-rank test was used. Categorical variables were tested with Fisher's exact test. Due to low case numbers, response rate differences and ostomy group correlations were only analyzed for weeks 12 and 24. Correlation analysis was assessed by Pearson coefficient; unadjusted r^2 values from simple linear regression are reported. A p-value of $p < 0.05$ was considered as statistically significant. In repeated measures analyses, we adjusted p-value for multiple testing using Bonferroni correction. If data along time axis were available in all individuals, within-subject effects were analyzed with repeated measure analysis of variance (Greenhouse-Geisser correction). Values are given as means $\pm$ SD.

3. Results

3.1. Patient characteristics

Baseline characteristics of 27 teduglutide-treated patients included in this cohort are presented in Table 1.

3.2. Teduglutide treatment characteristics

Of all 27 patients who started teduglutide treatment since October 2014, 21 were still undergoing therapy at the cut-off date of this analysis (for details see Table 2). While the approved standard dose was given to 89% of patients, a 50% dose reduction was applied in three patients with chronic renal failure including one case of end-stage renal disease as recommended. Teduglutide treatment was temporarily discontinued in seven patients (26%) due to adverse events and was permanently discontinued in three patients (11%). Almost all patients who had temporarily stopped treatment were able to restart teduglutide injection with either full or a 50% dose except of three patients, who are still planned to be re-exposed. In three patients, 50% of the initial dose was achieved by applying the "full" dose (0.05 mg/kg BW) every other day. Application modes at last follow up are listed in Table 2.

3.3. Functional response: PS requirements

At the time of analysis, six out of 27 patients had been treated with teduglutide for less than 12 weeks, two were excluded due to incomplete PS reduction documentation leaving 19 patients analyzed after 12, 24, 52, 78 and 104 weeks of teduglutide treatment with a median of 56 weeks on teduglutide (range 22—134 weeks). Most recent changes in calorie or fluid regimen were made at a median of 20 weeks prior to teduglutide initiation (range 0—118 weeks). Mean inter-subgroup baseline parenteral volume or kcal requirements normalized to kg BW/day were comparable (data not shown). In comparison with baseline values, significant overall reductions of fluid volumes and energy requirements were seen during each observation time (Fig. 1 and suppl. Table), ranging from about 20% IVF and PN reduction in patients treated for 3 months to about 45% reduction in patients treated for 2 years. This was accompanied by significantly reduced PN application frequency of approximately one and two PN days per week, respectively (Fig. 1c).

Almost all patients (90%; 17/19) showed reduced PS requirements: first volume reductions were made after a median of 10 weeks (range 1—19 weeks) and first calorie reductions after a median of 11 weeks (range 1—19 weeks). The number of responders (reduction of PS volume $\geq$ 20%, 15 out of 19 patients so far) at 24, 52 and 104 weeks on teduglutide was n = 10/17 (59%), n = 10/11 (91%) and n = 7/7 (100%), respectively (see Fig. 2a and Table 4); onset of response was between 1 and 45 weeks (Fig. 2b). Mean PS volume reduction from responders was 23% (range −20 to −100%), 44% (−33 to −100%) and 41% (−33 to −100%), respectively. An early volume response (reduction of PS volume $\geq$ 20% at 12 weeks of treatment) was observed in 9/19 (47%) patients (−29 to −100%) with five patients responding even before 12 weeks of treatment (Fig. 2b). Response rates in patients with colon in continuity (14/19, 74%) at week 12 (57%) and 24 (67%) were numerically higher than in ostomy patients (20% and 40%, respectively; p = 0.3 and p = 0.59 respectively). The number of responders at weeks 12 and 24 in the

Table 1
Demographic and clinical patient characteristics prior to teduglutide treatment.

Patient characteristics before teduglutide treatment	
Patients exposed to teduglutide (since October 2014), n	27
Female sex, n (%)	14 (52%)
Age, [years]	
Mean ± SD	51 ± 17
Median (range)	53 (21—82)
BMI, [kg/m²]	
Mean ± SD	21.3 ± 2.6
Median (range)	21.4 (15.3—27.2)
Cause of major intestinal resection, n (%)	
Vascular disease	12 (44%)
Inflammatory bowel disease	4 (15%)
Traumatic injury	3 (11%)
Postsurgical obstructive intestinal adhesions	4 (15%)
Other (volvulus, aganglionosis, perforated sigmoid diverticulitis)	4 (15%)
Duration of chronic IF, [years]	
Mean ± SD	4.3 ± 5.8
Median (range)	2.9 (0.6—23.3)
Patients with colon in continuity, n (%)	21 (78%)
No colon resection, n (%)	5 (24%)
Partial colon resection, n (%)	16 (76%)
Remnant small bowel length in patients with colon in continuity, [cm]	
Mean ± SD	45 ± 34
Median (range)	46 (0—140)
Unknown, n (%)	3 (14%)
Patients with stoma, n (%)	6 (22%)
Duodenostomy, n (%)	1 (17%)
Jejunostomy, n (%)	1 (17%)
Ileostomy, n (%)	3 (50%)
Descendostomy, n (%)	1 (17%)
Remnant small bowel length in patients with stoma, [cm]	
Mean ± SD	205 ± 173
Median (range)	150 (70—450)
Unknown, n (%)	2 (33%)
Revised ESPEN clinical classification [5]	
PN1, n (%)	6 (22%)
PN2, n (%)	9 (33%)
PN3, n (%)	8 (30%)
PN4, n (%)	4 (15%)
Prescribed total parenteral volume, [L/week]	
Mean ± SD	13.7 ± 7,9
Median (range)	11.2 (2—28)
Prescribed parenteral energy, [kcal/week]	
Mean ± SD	8300 ± 4700
Median (range)	8400 (0—15,300)
PN-days, [days/week]	
Mean ± SD	5 ± 2
Median (range)	6 (1—7)
IVF infusions, [number of fluid and electrolyte infusions/week]	
Mean ± SD	4 ± 4
Median (range)	4 (0—14)

Abbr.: BMI — Body mass index, IVF — Intravenous fluid, ESPEN — European Society for Clinical Nutrition and Metabolism, PN — Parenteral nutrition, SD — Standard deviation.

overall and colon in continuity group showed no statistically significant association with a shorter or longer duration of PS-dependent IF before teduglutide initiation (<2 years vs. >2 years; <3 years vs. >3 years; <5 years vs. >5 years; all p > 0.1). Also, no significant correlations between absolute IF duration and both absolute and relative volume reduction were detected at none of the treatment weeks and groups (all p > 0.062, all r² < 0.291). Median follow up time from non-responders (4/19) was 44 weeks (range 24—56 weeks).

Four patients (21%), who could be categorized at baseline into clinical categories "PN1" (<1000 ml total volume/day) and "PN3" (2001—3000 ml/day) according to modified ESPEN-classification of chronic intestinal failure [5], gained independency from PN after 23 weeks (range 12—37 weeks), two continuing on IVF (both "PN3") (Fig. 3).

3.4. Symptomatic response: stool characteristics

Baseline stool frequency ranged from 2 to 30 times per 48 h. After 12 ± 1 and 22 ± 3 weeks, patients demonstrated a significant reduction in stool frequency compared to baseline (p = 0.001; p = 0.002, respectively) (Fig. 4a). In parallel, stool consistency increased relatively with teduglutide treatment resulting in predominantly mushy or partly formed stools as compared to mostly liquid stools at baseline (Fig. 4b).

3.5. Nutritional status stability: BMI, BIA and serum albumin analysis

Nutritional status of teduglutide treated SBS-IF patients was regularly monitored by BW, BIA and blood parameters and was

Table 2
Teduglutide treatment characteristics.

Teduglutide treatment characteristics	Number of patients	Reasons for treatment decision	Number of events[a]
Initially 0.05 mg/kg BW/d	24 (89%)	Standard dose, no contraindication	
Initially 0.025 mg/kg BW/d	3 (11%)	Chronic kidney disease	2
		End stage renal disease	1
Temporary stop[b]	7 (26%)	Dyspnea due to hypervolemia	1
		Abdominal discomfort	1
		Low blood pressure	1
		Sepsis	1
		Intestinal surgery	1
		Pneumonia + endocarditis + worsening of kidney failure	1
		Nausea + malaise	1
		Lack of significant effect + cephalgia	1
Permanent stop (not included in temp. stop group above)	3 (11%)	Death, not teduglutide-related	1
		Suspected alcohol abuse	1
		End stage renal disease	1
Dose reduction (to 0.025 mg/kg BW/d)	9 (33%)	Weight increase	2
		Dyspnea due to hypervolemia	1
		Nausea + malaise	2
		Abdominal discomfort	2
		Rash	1
		Worsening kidney function	1
		Hypotension	1
Application mode at last f/u			
Daily initial dose	15 (56%)		
Initial dose e.o.d.	2 (7%)		
0.025 mg/kg BW/e.o.d.	1 (4%)		
0.025 mg/kg BW/d	3 (11%)		
Not exposed	6 (22%)		

Abbr. BW − Body weight, e.o.d. − every other day, f/u − follow up.
[a] More than one event per patient possible.
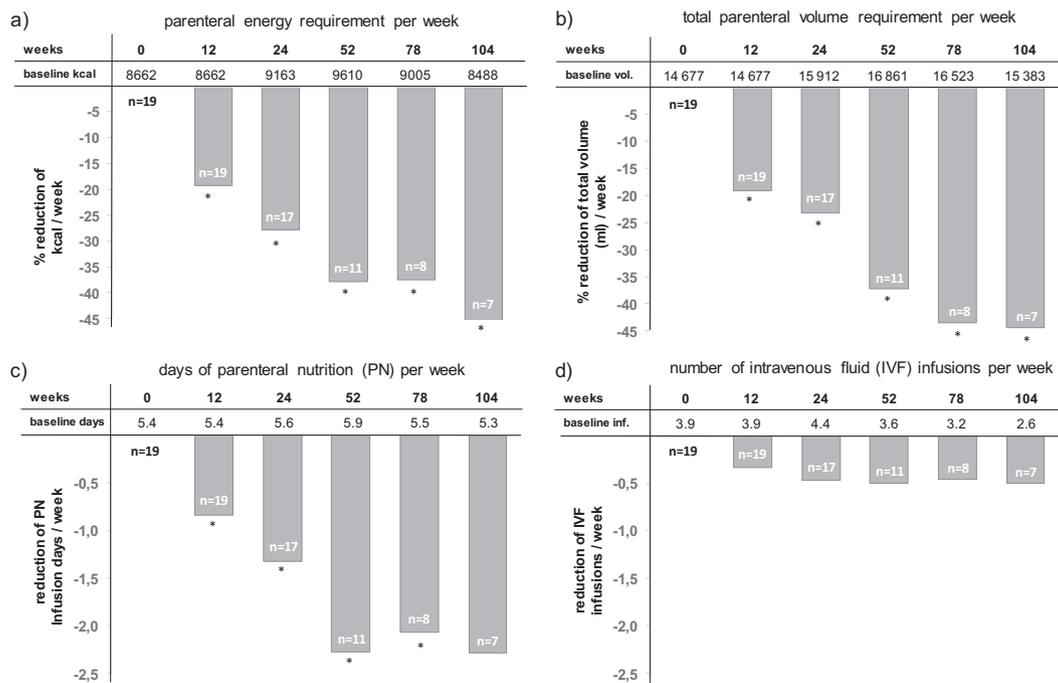[b] Subsequent dose modification possible.

Fig. 1. Reduction of PS requirements after 12 (n = 19), 24 (n = 17), 52 (n = 11), 78 (n = 8) and 104 (n = 7) weeks of teduglutide treatment. a) Parenteral energy requirement as % reduction of kcal/week, b) total parenteral volume as % reduction of total ml/week, c) days of parenteral nutrition (PN) per week, d) number of intravenous fluid (IVF) infusions (fluid and electrolytes only) per week. After Bonferroni correction, significant changes are indicated as: *p < 0.01 vs. basal values of each subgroup.

analyzed for patients with functional response (PS) analysis. Mean baseline BMI (±SD) was within the normal range in all patients (22 ± 2 kg/m², n = 19). In comparison to baseline, BMI increased significantly at week 12 (+0.8 kg/m², n = 19, p < 0.01), tended to increase or was stable at weeks 24 (+0.9 kg/m², n = 17), 52 (+0.8 kg/m², n = 11), 78 (+0.5 kg/m², n = 8) and 104 (±0 kg/m², n = 7) of treatment (p > 0.01, respectively). BIA measurement was performed when clinically appropriate and was available in eight patients after
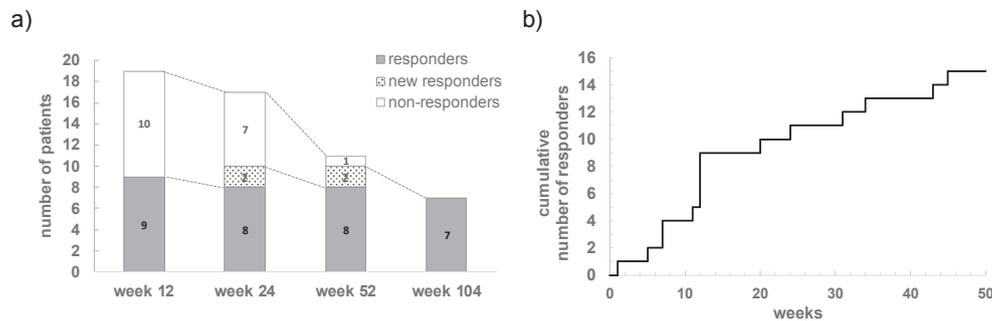
Fig. 2. Responders over time. a) Number of patients with reduced PS volumes ≥20% (responders) and ≤20% (non-responders) at 12, 24, 52 and 104 weeks on teduglutide. New responders describe patients, who became responders after being classified as non-responders at the previous time point of analysis. b) Onset of clinical response (PS volume reductions ≥ 20%) as cumulative analysis from all responders (n = 15/19).
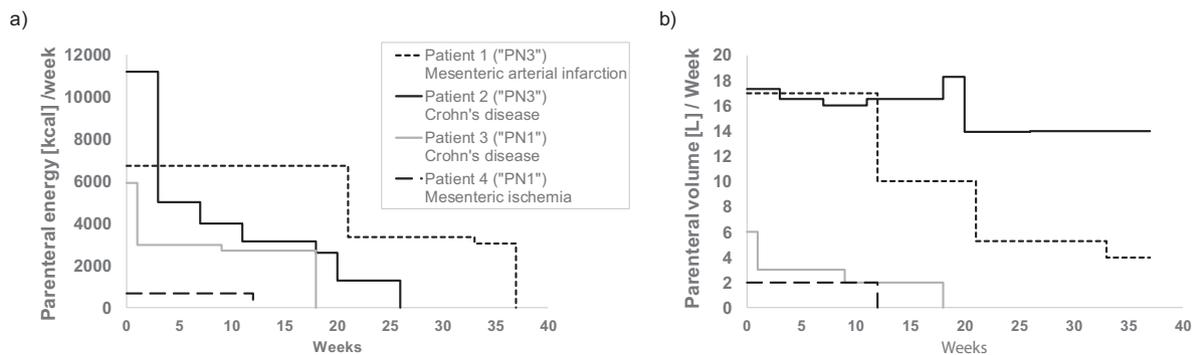

Fig. 3. Individual reduction of a) parenteral energy requirements and b) volume requirements per week of patients who gained complete independence from parenteral nutrition. Abbr.: PN − parenteral nutrition, see ESPEN classification of chronic intestinal failure [5].
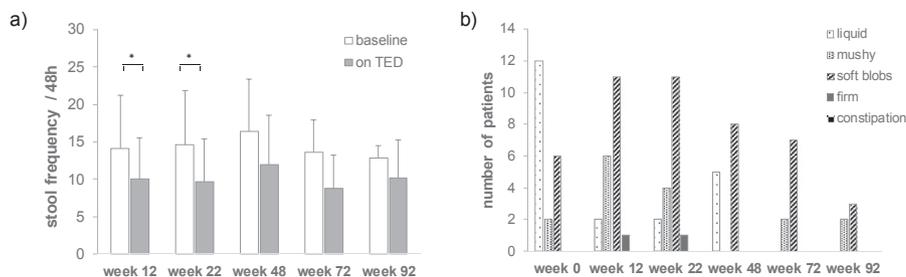

Fig. 4. Stool characteristics improved with teduglutide treatment after 12 ± 1 weeks (n = 20), 22 ± 3 weeks (n = 18), 48 ± 7 weeks (n = 13), 72 ± 7 weeks (n = 9), 96 ± 6 weeks (n = 5). a) Stool frequency, white bars representing stool frequency at baseline, grey bars representing stool frequency after 12–92 weeks. b) Stool consistency, bars representing number of patients with liquid stool (▤), mushy stool (▦), soft stool (▨), solid stool (■), and constipation (▧). Data are given as mean ± SD; after Bonferroni correction, significant changes are indicated: *p < 0.01 vs. baseline.

both 6 months and one year on teduglutide. Baseline BIA measurements of two patients had to be excluded due to abnormal raw impedance data and remaining baseline BIA measurements were done 1−13 weeks before teduglutide initiation. Nutritional status analysis demonstrated stability without significant deviations in BMI (p = 0.2), phase angle α (p = 0.4), body fat (p = 0.2), body cell mass as % of lean body mass (p = 0.5), intracellular water (p = 0.4) and extracellular water (p = 0.4) at weeks 24 ± 4 and 50 ± 4 (n = 6, Fig. 5), although parenteral calories and fluids/week had been reduced by 55% and 47% at week 24 and 57% and 54% at week 50, respectively. Further, serum albumin levels revealed no significant difference to baseline values and stayed within the normal range after 26 ± 4 weeks and 51 ± 4 weeks (n = 6; baseline 42.8 g/L vs. 26 weeks 41.8 g/L, and 51 weeks 41.2 g/L; p = 0.6).

3.6. Structural response: small intestinal mucosal morphometry and systemic citrulline release

In 24/27 patients a small intestinal biopsy had been obtained during endoscopy from the upper jejunum/distal duodenum and was analyzed for structural abnormalities, which were not observed in any of the cases prior to teduglutide initiation. Biopsies for histological reevaluation of morphological changes after roughly one year of treatment were available in 10 patients.

After 61 ± 17 weeks on teduglutide, significant increase in villus height and crypt depth compared to baseline was observed (Table 3). Analysis of plasma citrulline levels at baseline versus week 26 ± 6 and 51 ± 13 also showed a significant increase in teduglutide-treated patients (Table 3).
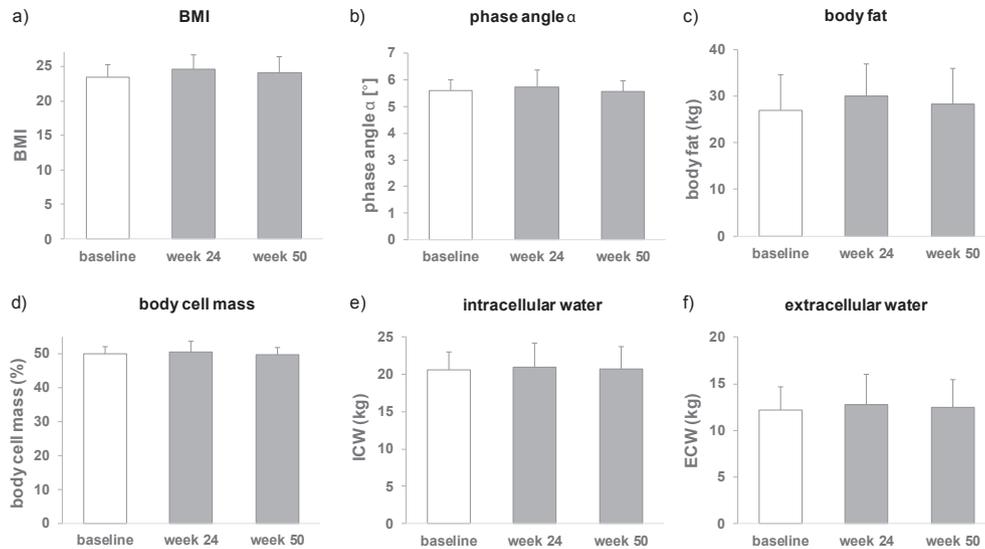
Fig. 5. BMI and body composition analysis demonstrated stability of nutritional status after 24 ± 4 weeks and 50 ± 4 weeks of teduglutide treatment (n = 6). a) Body mass index [kg/m^2], b - f) as measured by BIA: b) phase angle α [°], c) body fat [kg], d) body cell mass as % of lean body mass, e) intracellular water (ICW), f) extracellular water (ECW).

3.7. Adverse events

Adverse events (AE) were recorded on a routine basis either during nurse visits at home or during office visits in the outpatient clinic and recorded as reported. Gastrointestinal AEs such as abdominal distension incl. flatulence (11/27; 41%), abdominal pain (9/27; 33%), and nausea (8/27; 30%) were the most frequent and spontaneously clinically improving or resolving AEs within the initial treatment phase. Other more than singular AEs were injection site reactions (4/27; 15%), headaches (5/27; 19%), upper respiratory tract infections (5/27; 19%), clinical signs of volume overload such as edema (6/27; 22%) and stoma nipple hypertrophy (3/6; 50%). Concomitant medications had to be adapted in 6/27 patients (22%) and for 15 treatments. Adverse events were in no patient the cause of permanent discontinuation of teduglutide, however transient dose reduction, teduglutide interruption or injection interval lengthening were applied in 9/27 cases (33%) due to AEs (see Table 2). All patients had undergone screening colonoscopy prior to teduglutide initiation and regular annual follow-up colonoscopies with hitherto no signal for colorectal polyp/adenoma growth.

4. Discussion

This analysis of teduglutide treatment in a clinical setting demonstrated functional, symptomatic and structural effects of teduglutide with long-term stability of nutritional status despite teduglutide-induced PS reductions and revealed new insights into teduglutide application in routine medical care from a European, monocentric SBS-IF cohort.

The most important intended effect of teduglutide-enhanced intestinal adaptation is reduction of PS including fewer days on PS, ideally enabling complete weaning from PS. However, the latter was only achieved in approximately 12% of patients in clinical trials and 61% in a small, US single center cohort of long-term teduglutide-treated patients thus far [32,34]. Our results show that 4/19 (21%) patients could be weaned off of PN, with 2 of the 4 remaining on IVF for subjective reasons; therefore complete weaning off rate in our clinical setting (2/19, 11%) is similar to that of previous clinical trials [32], most likely due to strict patient selection criteria which resembled those of the teduglutide phase III approval trials.

Several PS characteristics were significantly reduced in our real-life cohort (Fig. 1). A decrease of at least 20% in PS volume is considered clinically beneficial and patients with successful PS reduction to or beyond this threshold are termed "responders" [25,28]. In the phase III trials, 46% [25] and 77% [28] of patients were responders at 20 and 24 weeks (see Table 4). The second phase III trial [28] allowed earlier and more aggressive volume reductions, possibly explaining the higher responder rate. In our clinical cohort, the responder rate of 59% lies in between. An explanation for this may be the personalized PS volume reduction in routine clinical practice. The apparent greater teduglutide responder rate and volume reduction in our clinical setting at weeks 52 and 104 can be explained by a shorter treatment duration of non-responders compared to responders (Table 4 and Fig. 2a). Interestingly, larger baseline PS volumes in routine medical care coincide with larger absolute volume reductions as compared to clinical trials in 4 out of 5 cases (Table 4). This correlation was also described in a post hoc analysis of etiology- and bowel anatomy-related teduglutide treatment success [33]. Therefore, differences in absolute volume reductions between routine medical care and controlled trials (see Table 4) may also be due to patient selection with higher baseline volume requirements in the real-life cohort representing differences in average bowel anatomy [33] and/or differing PS weaning strategies.

An earlier onset of response was seen in 47% of patients, showing a parenteral volume reduction ≥ 20% within 12 weeks of treatment (Fig. 2a,b). This emphasizes both the early effectiveness with improvement of intestinal fluid absorption and the importance of structured clinical monitoring during the initial phase of teduglutide treatment. The fact that additional responders were also seen beyond 24 weeks of treatment (5/15, 33%; Fig. 2b), supports the idea of a heterogeneous functional response to teduglutide treatment in SBS-IF. A cumulative effect over time has been proposed to explain late responses [32]. A potential delayed clinical response until up to 104 weeks of treatment has been described in the clinical trials [30,31], suggesting treatment durations in formal non-responders beyond 24 weeks based on case-by-case decision by physicians [31]. As it is not yet clear whether

the current non-responders in our cohort will become so called "slow responders" and clinical or molecular response predictors have not yet been identified, further individual follow up may contribute to understand the underlying mechanisms of a delayed response [31].

The vast majority of naturally occurring intestinal rehabilitation is observed within the first two years after surgery and a colon in continuity is favorable for the development of PS independence [13,14,16]. Also, the analyses of PN-independent patients after teduglutide exposure in clinical trials suggest a beneficial effect of a colon in continuity in the weaning process [32,41]. Because in most teduglutide treated patients of our routine medical care cohort colon was in continuity and in 42% of them IF duration was below 2 years (14% < 1 year), some of these patients might still have spontaneously presented with a diminishing need for PS over time even without teduglutide [13,14,16]. Therefore, we analyzed the degree of responsiveness according to continuity status and IF duration. Although responder rates were numerically higher in the colon in continuity group compared to ostomy group, this did not reach statistical significance. Furthermore, no significant association between the number of responders and an either shorter or longer IF duration in the overall and colon in continuity group was observed. In addition, no correlations between the duration of IF and the amount of absolute and relative reduction in PS volume were detected, neither in the overall nor in the colon in continuity cohort. These results and an additional early response even in patients with a long duration on PS argue for a specific, pharmacologically induced intestinal adaptive effect caused by teduglutide, although spontaneous, naturally occurring adaption may still have contributed to some degree, which cannot be quantified in the analyzed clinical setting. Development of predictive biomarkers might help to clarify this situation and assist in GLP-2 analog treatment management in the future. In this analysis small bowel length was not included as a potential factor influencing adaptive response [13,14,42] because it has failed as a predictor for teduglutide-induced effects as shown in a post hoc analysis of STEPS-trial results [33].

Besides parenteral volume, parenteral calories per week were also significantly reduced by either reduction of calories per infusion bag and/or infusions per week. Reduction in parenteral energy requirements was also observed in the phase III clinical trials to varying degrees [25,30]. For SBS-IF patients, a reduction of PN days and PN calorie amounts is meaningful for several reasons: Firstly, as non-aseptic manipulation of the central catheter device may lead to catheter-related bloodstream infections (CRBSI) [43] and as the amount of parenteral calorie intake is an independent risk factor for CRBSI in patients receiving parenteral nutrition [44], the risk for CRBSI in teduglutide-treated patients may be reduced by decreased hub manipulations per week and less calories applied; however, direct proof of this concept is not yet available. Secondly, a reduction in PN macronutrients may reduce the risk of intestinal failure associated liver disease (IFALD), which is partly nutrient-related [45]. Thirdly, since PN is a time consuming procedure [46] and especially a reduction of intravenous energy and amino acids results in a decreased infusion time, less time on PS is likely to improve patients' quality of life (QoL) [47]. While days on PN were significantly reduced, IVF infusions per week remained mostly stable with a trend towards reduction (Fig. 1c,d). This can likely be explained by i) unchanged IVF application frequency with or without volume adjustments and ii) on the one hand decreased IVF infusions/week in some patients due to improved absorptive capacity but on the other hand additional IVF infusions/week in some individuals who reduced PN but still needed compensation for fluid deficits on PN-free days. As for complete PS weaning and PS volume reduction, patient selection and individual weaning regimens have

been more personalized in our routine medical care compared to PS-weaning scheme in clinical trials [25,28,30,31,33].

Four patients from our cohort have become independent from PN to date. Two patients, who initially needed a low amount of PS with <1000 ml per day (classified as PN1) and whose small bowel remnant is unknown but with partial colon in continuity, are also completely independent from IVF. Similar cases of achieved enteral autonomy have been described [32,34] and both patients support the hypothesis, that patients with low baseline PS volume requirements are most likely to be completely weaned off [34]. Two patients with high baseline infusion levels (PN3) gained independence from PN but are still dependent on some IVF (FE2). Both initially gained weight under teduglutide therapy. After independence from PN, patients lost weight below baseline levels but BMI was still within the normal range (data not shown). One of the two returned to full time work. The other patient suffered from central venous port-related infection and pyloric stenosis accompanied by anorexia, which may partly explain weight reduction. Individual cases of weight loss after PN independence were also observed in the clinical extension trials of STEPS [32], as well as in first real-life data [34] and "weight decrease" was reported as a common AE in 25% of patients [31], although this is a consequence of treatment success (PN reduction) and without any evidence of harm if patients were appropriately monitored. Resumption of PS during periods of intercurrent illness has also been described [34]. As SBS-IF patients cannot compensate short-term weight loss by hyperphagia, this is an important issue in weaned-off SBS-IF patients and is one of several reasons why these patients still need to remain within a structured monitoring program [4].

With regard to clinical symptoms, this report describes for the first time clinically measurable effects of teduglutide on stool characteristics in SBS-IF patients. Especially for but not limited to ostomy patients, reduced intestinal outputs may be of meaningful importance to improve QoL [48,49]. The majority of our patients reported decreased bowel movements and improved stool consistency, despite unchanging antidiarrheal treatment. Until now, fecal excretion evaluation is limited to a complex balancing study [24], which is not feasible in a clinical setting, or only indirectly described by fluid composite effect [18,25]. The described teduglutide-mediated increase in intestinal wet weight absorption [24] is a relevant explanation for observed improvements in stool frequency and consistency but decreased secretions and decelerated motility may also contribute and deserve further investigation [8].

Nutritional status, which is an important clinical outcome of patients at extremely high risk of malnutrition and its sequelae, remained constant in spite of reduced PS in our cohort. Serum albumin, as a complement to a thorough nutritional status examination [50], remained stable while BMI tended to increase slightly during teduglutide treatment, especially during the initial phase of treatment. This may have been related to increased fluid absorption [24], but has not yet been assessed by BIA. BIA data analysis in a subset of our cohort revealed that phase angle α, body cell mass, along with intracellular and extracellular water, remained constant after both 6 months and one year. This suggests a stable amount and quality of soft tissue and stable hydration status despite the reduction of calorie and IVF support. During a phase III trial, body composition was assessed by Dual Energy X-ray Absorptiometry (DEXA), which showed a significant increase in body weight, mainly confined to lean body mass [25]. Compared to DEXA, BIA is an easy-to-use tool to monitor body composition at frequent time intervals in the clinical setting in order to distinguish between changes in body fat, lean body mass and body water in healthy subjects [51] and is used in SBS-IF
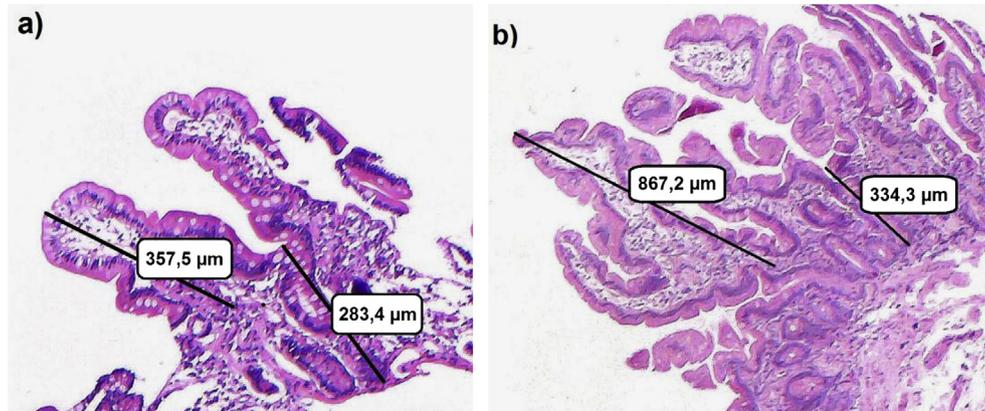
Fig. 6. **Representative small intestinal biopsy of one single patient a) before teduglutide treatment and b) after 60 weeks of teduglutide treatment**. Hematoxylin and eosin staining, original magnification a) ×40, b) ×16.

patients [29]. As BIA has its limitations in subjects with altered hydration status [52,53] and teduglutide has the potential to enhance fluid uptake and augment body fluid content (e.g. visible as peripheral edema) [24], further studies of BIA applicability and its raw parameters use especially to monitor the initial phase of teduglutide treatment, are warranted.

Teduglutide's effects of enhanced intestinal adaptation have been proposed to be mediated by structural and molecular effects on intestinal mucosa, particularly in the small intestine [8,24,25]. In this study, we were able to demonstrate structural effects of the GLP-2 analog teduglutide on small intestinal mucosa in a subset of patients resulting in hypertrophy with significantly increased villus height as well as crypt depth (Table 3 and Fig. 6). This has been previously observed in animal models of SBS, healthy humans and SBS-IF [24,25,54]. Furthermore, citrulline, a non-essential amino acid of arginine metabolism, which is synthesized in enterocytes, has been shown to be a direct surrogate marker for enterocyte mass, particularly in adults and children with SBS [27]. A significant

increase in serum citrulline, comparable to STEPS-trial data [26], has been observed in the studied cohort, suggesting a role not only as a proof of treatment concept but also as a predictive marker of response to treatment.

Many limitations of our study are related to its retrospective, monocentric and uncontrolled nature, however, this is an appropriate approach to collect and analyze data in a rare disease for which cumulative information is otherwise difficult to achieve. As data acquisition was purely observational i) data record may not be entirely complete which may have lead to under-reporting, ii) higher variations in measurement results compared to measurements in a controlled trial setting or missing values due to retrospectively defined analysis time points were possible. The number of cases especially in subgroups may limit general-ization of statistical significance interpretation and limit comparability to clinical trial results although similar sample sizes in teduglutide treated SBS-IF cohorts are common [24,34]. On the other hand, highly selective patient inclusion in clinical trials may also introduce a bias as compared to routine clinical practice; thus, studying clinical practice contributes importantly to the validation of clinical trial results and their real-life applicability.

It should be mentioned that teduglutide, which is approved as an orphan drug, is an expensive treatment [55,56]. Despite recommendation by the European Society for Clinical Nutrition and Metabolism Guidelines [4], its reimbursement also depends on national regulatory affairs. Consideration of overall costs and potential or expected benefits in the orphan indication setting of SBS-IF as well as an estimation and repeated reassessment of the expected individual risk-benefit ratio are advisable [4]. This is of particular importance when a patient does not respond to treatment as expected; however, the possibility of late

Table 3
Increase in villus height, crypt depth and plasma citrulline levels after teduglutide treatment.

	n	Baseline	Teduglutide exposure	p Value
Villus height (μm)				
Week 61 ± 17	10	570 ± 191	805 ± 235	0.021
Crypt depth (μm)				
Week 61 ± 17	10	278 ± 61	349 ± 92	0.01
Plasma citrulline (μM)				
Week 26 ± 6	9	16.5 ± 7.7	31.9 ± 14.6	0.001
Week 51 ± 13	8	16.6 ± 8.2	38.6 ± 26	0.008

Data are given as mean ± SD.

Table 4
Comparison of responder rates (≥20% reduction in PS volume (vol.)) and PS volume reductions (%) in patients treated with teduglutide in routine medical care compared to clinical trials.

	Routine medical care			Clinical trials			Ref.
	Baseline PS vol./week	Responders	Mean PS vol. reduction/week	Baseline PS vol./week	Responders[a]	Mean PS vol. reduction/week[a]	
Week 24	15.9 L	59%	−3.7 L (−23%)	9.6 L	46%	−2.5 L (−26%)	[25]
				12.9 L	77%	−4.4 L (−32%)	[28]
Week 52	16.9 L	91%	−6.3 L (−37%)	9.8 L	68%	−4.9 L (−52%)	[30]
Week 104	15.4 L	100%	−6.8 L (−44%)	10.4 L	55%	−3.1 L (−28%)	[31],[b]
				12.8 L	67%	−4.0 L (−39%)	

[a] Dose group of 0.05 mg/kg/d and reductions (%) as provided by authors, if available.
[b] Two treatment groups (0.05 mg/kg/d) had a total treatment period of 104 weeks [31].

responders with a significant response even after 24 months [31,32] should be kept in mind prior to defining non-response in any given patient.

5. Conclusions

Teduglutide is an effective treatment for PS-dependent SBS-IF. However, SBS-IF is characterized by a heterogeneous patient group with a rare (Orphanet-IDs: 2301, 95427, 104008, 365563) but complex clinical condition [57]. Frequent gastroenterological/nutritional consultations, especially during initial teduglutide treatment, have shown to be important for patient stability and appropriate volume and nutrition management due to varying comorbidities, side effects and/or time and effect range of response due to both variable intestinal anatomy as well as adaptation. The group average analysis of clinical data on long-term use of teduglutide for strictly selected and stable SBS-IF patients demonstrates improved intestinal function due to increased fluid and nutrient absorption, shown by decreased PS, decreased stool frequency and increased stool consistency. Subgroup analysis showed that parenteral energy and volume support was reduced at no cost of nutritional status. Further multicentric and even more long-term analyses also looking into long-term outcomes such as complications from PS (e.g. CRBSI) or PN (e.g. IFALD) as well as overall survival will contribute to the understanding of effectiveness as well as cost-effectiveness of this significantly effective and promising but resource-intense treatment option of this orphan condition.

Statement of authorship

The authors' responsibilities were as follows: SP, UFP conceiving and writing of the article, acquisition of data, analysis and interpretation of data, literature research; MK, BK-D, JB: Data analysis; AR, SM, DT, HB, EB, VAM, AP, KHW, BW acquisition of data; SM, BK-D literature research; KHW, SM, MK, BK-D, BW, EB, DT, VAM, AP, AR, HB, JB: critical input and revision of the manuscript. All authors read and approved the final manuscript.

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Conflicts of interest

UFP has been a site investigator of the STEPS-trial and has received advisory board and lecture honoraria from NPS Pharmaceuticals and Shire Pharmaceuticals as well as research funding from Shire Pharmaceuticals. AP and SM have received advisory board and lecture honoraria from Shire Pharmaceuticals.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.07.030.

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