Predictors of response and enteral autonomy in children with short bowel syndrome treated with teduglutide: a real-life multicentre cohort study

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Summary

Background Teduglutide (TED), a glucagon-like peptide 2 analogue licensed for children with short bowel syndrome (SBS), is increasingly used in the attempt to augment intestinal absorption and lower parenteral nutrition (PN) needs. Data from real-life studies on TED efficacy and predictors of response in children with SBS are limited. This study aimed to define pre-treatment and on-treatment predictors of response, in terms of PN reduction and weaning, in TED treated children with SBS.

Methods In this multicenter cohort study, we collected retrospective and prospective data of children with SBS undergoing TED treatment in 7 countries in Europe (Italy, Spain, Croatia, Germany, France, Israel, Portugal). All children with SBS starting TED treatment and not included in clinical trials were eligible. Information on patients' post-surgical anatomy, amount of PN calories and volume required at baseline and at 3, 6 and 12 months after TED start, along with biochemical markers of PN tolerance and complications, were recorded. The main outcome was predicting factors of 1 year response to TED treatment defined as a reduction of ≥20% of PN needs.

Findings Between 01.06.2021 and 31.05.2023, we collected information on 104 children (64 males, 61.5%; 40 females, 38.5%) the median age at enrolment was 6.7 years old (IQR: 3.6–10.4); at 12 months' follow up after TED start 68 children achieved response (cumulative incidence: 70%, 95% CI 61%–79%), whereas complete PN weaning was achieved in 21 children (cumulative incidence: 22%, 95% CI 15%–31%). Multivariable logistic regression analysis showed that predictors of response were longer residual small bowel length (p = 0.027), higher weight Z-score at baseline (p = 0.0061) and normal liver enzymes (p = 0.010). Pre-treatment PN calories <35 kcal/kg/day (p = 0.044) and citrulline ≥14 μmol/L (p = 0.047) predicted complete PN weaning, as well as haemoglobin and citrulline rise in the first 6 months of treatment (p = 0.014 and p = 0.044 respectively).

Interpretation In children with SBS, longer residual small bowel, better nutritional status and absence of liver disease were associated with response to teduglutide. Complete PN weaning was predicted by lower calories needs and higher citrulline at baseline. An increase of haemoglobin and citrulline in the first 6 months of treatment were further predictors of complete PN weaning. Even if limited by the real-life design of the study, these findings may guide a tailored indication for the use of teduglutide in children with short bowel syndrome.

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Keywords: Intestinal failure; Parenteral nutrition; Haemoglobin; Liver function

Research in context

Evidence before this study

We searched PubMed for studies published between 01.03.2015 and 01.03.2025, using the search terms *teduglutide*, *GLP-2 analogues*, *children*, and *short bowel syndrome* in abstracts, titles, or MeSH headings. Additionally, we reviewed the references cited in the identified papers. Evidence from clinical trials demonstrated a 65% response rate to teduglutide treatment, with a 10% rate of parenteral nutrition (PN) weaning. These findings were subsequently supported by single-center real-world retrospective studies, which reported variable rates of response and PN weaning. Cost-effectiveness analyses comparing the standard of care for short bowel syndrome patients on parenteral nutrition with teduglutide treatment have highlighted the higher costs associated with the drug. Based on this evidence, it would be beneficial to identify patient-related characteristics that could predict treatment response and successful PN weaning.

Added value of this study

This study provides additional information on pretreatment factors predicting the response to TED treatment in a real-world setting with a multicentre population. It also identifies both pretreatment and on-treatment factors that predict complete weaning from parenteral nutrition (PN).

Implications of all the available evidence

Pretreatment factors and on-treatment markers of PN weaning may help identify the most suitable candidates for treatment and guide early discontinuation in the absence of response predictors. A more patient-tailored approach could improve the cost-effectiveness of TED use. The observation that a mild increase in liver function tests may predict non-response warrants further investigation into the role of liver disease in TED efficacy in this setting. Additionally, an increase in haemoglobin levels could serve as a practical and cost-effective indicator of which children may successfully wean off PN. However, these results should be interpreted with caution, as they are derived from a multicentre study with non-standardised care and variable criteria for treatment candidacy in SBS children.

Introduction

Paediatric short bowel syndrome (SBS) is a malabsorptive condition usually following surgical intestinal resection due to congenital (e.g. Hirschsprung disease, gastroschisis, intestinal atresia and stenosis) or acquired (e.g. necrotizing enterocolitis, volvulus) conditions. SBS leads to various degrees of intestinal failure with consequent need for parenteral nutrition (PN) support, sometimes life-long.[1]

A recent study on a large cohort of patients with intestinal failure demonstrated the safety profile of long term PN.[2,3] However, severe and possibly life-threatening complications, including catheter-related bloodstream infections, loss of central venous access, liver disease, and metabolic bone disease, remain prevalent and result in impaired quality of life and survival.[4] Patients presenting with these complications could be classified as patients with nutritional failure.[5] Furthermore, although most children with SBS get weaned off PN, about 30% remain on PN without any possibility to reach intestinal sufficiency apart from considering intestinal transplantation.[6,7]

Therefore, new drugs have been developed to promote intestinal absorption.[8] Glucagon-like peptide (GLP)-2 is an intestinal growth hormone that increases crypt epithelial proliferation, reduces epithelial apoptosis, enhances visceral blood flow, amplifies nutrient absorption, and slows proximal intestinal motility.[9] Teduglutide (TED), a GLP-2 analogue with resistance to *in vivo* degradation, expands the absorptive intestinal epithelium by significantly increasing villus height in adult patients with SBS.[10]

Studies in adults have demonstrated the efficacy and safety of TED in the treatment of SBS.[11,12] In children with SBS clinical trial of 12-weeks treatment with TED showed, good tolerance and trends toward reduction in PN requirements paralleled by advancements in enteral nutrition (EN) feeding.[13] Based on this evidence, TED was licensed and became available on the market for the treatment of SBS in adults and in some countries in children.[4] In 2018, three studies focused on the daily use of TED in adults.[14–16] In total, these studies described 59 patients with a wide variability in response. In those studies, patients with at least some residual colon and an ileo-ileal or ileocolonic anastomosis (SBS types 2 and 3) responded better to TED treatment. All three studies seemed to agree on a slower response of treated adults compared with previously

published clinical trials,[11,12] describing significant improvements even after 6–12 months of treatment in some patients. Considering these results, these studies raised the issue of sustainability of TED costs and suggested the need for larger, "real-life" studies to determine its efficacy.

Recently, two pharma-economic models were published to assess the impact of TED treatment on PN requirements and global costs; they both agreed that, although reducing PN costs, TED costs had a high impact on overall expenditures for SBS patient care.[17,18]

In children there are no large studies focusing on predictors of response to TED in a real life scenario, allowing to unravel the issue of cost effectiveness at pediatric age. For these reasons, we planned a retrospective and prospective inception cohort study of children with SBS treated with TED in different European countries.

The primary aim of this study was to assess the rate of response (defined as in previous clinical trials: PN reduction of at least 20% from PN needs before treatment[19]) and the rate of complete PN weaning after 52 weeks of "real-life" treatment. Furthermore, we aimed to define possible predictors of response at diagnosis and during a 12 months' follow-up. The secondary aim was to report the safety of TED treatment based on the adverse events recorded during the treatment period.

Methods

Study design and participants

For this multicenter, observational, longitudinal, retrospective and prospective cohort study, an online registry was created to provide a safe and validated repository in which data were completely anonymised. Patients' records were visible only to the responsible clinicians, to the PI, and to the data manager.

The registry collected data retrospectively (children already treated but not included in clinical trials before the year 2021) and prospectively (study period 2021–2023) from European centers taking part in the Network of Intestinal Failure and Transplantation in Europe (NITE).

Inclusion criteria were as follows: patients <18 years old with SBS, dependent on PN and treated with TED; exclusion criteria were: other concomitant intestinal pathologies possibly affecting the endpoint evaluation and children previously enrolled in clinical trials.

As for TED treatment indications all children who started treatment needed to be stable with their PN needs for at least 3 months.

Procedures

Data were collected at baseline (just before starting the treatment) and every 3 months during treatment for up to 12 months; we included also the evaluation performed 3 months after the end of treatment, if the treatment was stopped.

Data collection included:

- Patient characteristics including the cause of SBS, type of SBS, date of the last major intestinal resection, length of residual small bowel and colon, and presence of the ileo-cecal valve,
- Anthropometric data (weight and height expressed in Z-score),
- PN dependency (PN calories and PN volumes and days/week on PN) including parenteral nutrition dependency index (PNDI) calculation (dividing total parenteral energy by estimated resting energy expenditure),[1]
- Oral and enteral calories,
- Input-output balance,
- Biochemical parameters (complete blood count, albumin, urea and electrolytes in blood and in urine, HCO3-, prealbumin, ferritin, AST, ALT, GGT, bilirubin, citrulline, fecal occult blood),
- Any adverse events,
- Concomitant drugs (antidiarrhoeic, antibiotics, electrolyte or vitamin supplementations).

An adverse event-specific form was completed in cases of severe adverse events. The last record included the reason for discontinuing the treatment. A sample file with all data collection forms included in the electronic database is provided in Supplementary Material.

Response to treatment was defined as the reduction in PN need of at least 20% of volume and/or calories from PN needs before treatment start.[19] Weaning from PN was achieved when children could safely stop PN support at any time during the 52 weeks follow-up period. Sustained weaning meant that from the time patients were weaned from PN none of them restarted PN during the 52 weeks of study period. Liver dysfunction was defined as AST >40 IU/L and/or ALT >40 IU/L and/or GGT >30 IU/L.

Data were analyzed after the first 52 weeks of treatment.

Demographic data and biochemical parameters were stratified according to the achievement of TED response and weaning off PN in the first 52 weeks of treatment.

Modification in all biochemical parameters during the first 6 months was stratified according to 1 year TED response and PN weaning in order to define which modification might predict response to treatment.

The study was approved by local ethical committee of the coordinating center in Bergamo (319/20) and then by all centers according to local regulations. Informed consent was obtained by the legal guardians before enrolment.

The study design adheres to the STROBE guidelines for observational studies.

Statistical analysis

Descriptive statistic was used to summarise patients' characteristics at baseline. Continuous variables were summarised as median and interquartile range, and categorical variables were presented as frequencies and percentages. Characteristics of the study population were stratified for 1-year response to treatment, and differences between groups were tested using the $\chi 2$ test (or Fisher's exact test, where appropriate) or the rank-sum test for categorical or continuous variables, respectively.

Cumulative incidence of response/PN weaning was estimated by the Kaplan–Meier approach: the log-rank test was used to test differences between groups.

A multivariable logistic regression model was applied to estimate the predictors of response/PN weaning. To identify the core variables, we applied a stepwise-backward regression model (p for removing ≥ 0.10), which included significant predictors of the outcomes resulting from univariate analysis, demographic characteristics, and clinically relevant variables. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) are reported. Where appropriate, continuous variables were dichotomised based on the cutoff identified by the Receiver Operating Characteristic (ROC) curve analysis. In particular, the optimal cutoff value was identified using the Youden index, which maximises the sum of sensitivity and specificity.

Trends of biochemical parameters over time were tested between groups (responders vs. non responders or PN weaning vs. no PN weaning) with linear mixed-effects models for repeated measures with group, time and group–time interaction as fixed effects and patient as random intercept (to account for patient variability).

A significance level of $p < 0.05$ was used. Statistical analysis was performed using STATA software, release 16.1 (StataCorp LP, College Station, TX, USA).

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

All investigators had access to data of their own centre and aggregate data. Full access to data was granted to principal investigators LN, AG, and LD which had final responsibility for the decision to submit for publication.

Role of fundings source

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Results

Treatment response and weaning rates

A total of 104 children (64 males, 61.5%) from seven different countries (Italy, Spain, France, Israel, Croatia, Germany and Portugal) were enrolled in the study. Median residual small bowel length was 25 cm (IQR: 15–45) and the median age at TED start was 6.7 years (IQR: 3.6–10.4). Demographic characteristics of the cohort are described in Table 1.

Overall, in children with SBS enrolled in the study, a clinical response to treatment was achieved in 57/104 (54.8%) after 6 months and in 68/104 (65.4%) after 12 months of treatment with TED corresponding to a cumulative incidence of 70% (95% CI 61%–79%). Of the

Demographics	Total
	N = 104
Male	64 (61.5%)
Female	40 (38.5%)
Age at TED start (years, median, IQR)	6.7 (3.6–10.4)
Ethnicity	
Caucasian	87 (83.7%)
Latin/Hispanic	5 (4.8%)
African	5 (4.8%)
Arab	7 (6.7%)
Week of gestation at birth (median, IQR)	33.0 (30.0–34.0)
Term	37 (35.6%)
N° of missing observations	*42*
Major causes of short gut	
Volvulus	23 (22.1%)
Necrotizing enterocolitis (NEC)	29 (27.9%)
Hirschsprung	15 (14.4%)
Gastroschisis	15 (14.4%)
Intestinal atresia	11 (10.6%)
Ischemic	5 (4.8%)
Pseudobstruction	2 (1.9%)
Meconium Ileus	1 (1.0%)
Mixed form	3 (2.9%)
Length of residual small intestine (cm, median, IQR)	25.0 (15.0–45.0)
N° of missing observations	6
Ileocecal valve	24 (23.1%)
Colon	88 (84.6%)
Type of SBS	
I	16 (15.4%)
II	64 (61.5%)
III	24 (23.1%)
Ending stoma	21 (20.2%)
Age at PN start (months)	0.5 (0.1–2.9)
Time from PN start-TED start (years, median, IQR)	5.9 (2.8–8.8)
Funding body of TED	
National Health Service	89 (100.0%)
N° of missing observations	*15*

Table 1: **Demographic characteristics of the cohort.**

68 responders at 1 year, 78% had an early response at 6 months compared to 11% of the 36 non-responders at 1 year (chi-squared test p < 0.001) (Table 2).

Moreover, complete PN weaning was achieved in 21 children after 12 months (cumulative incidence: 22%, 95% CI 15%–31%).

Response rate dynamics is expressed in Fig. 1 while PN weaning dynamics in Fig. 2. Most early responders maintained their response over time with an overall increase in response during the entire study period.

Demographic characteristics of PN weaned patients are described in Supplementary Table S1.

Early predictors of response to treatment after one year

According to the univariate analysis, a longer length of residual small bowel (p: 0.058), a higher weight Z-score (p:0.0028), a higher BMI Z-score (p:0.016), higher urea (p:0.037) and absence of liver dysfunction (p: 0.019) were predictors of 1-year response. Presence of the colon was not shown to predict response to treatment.

The potential effect of study center was tested in a logistic regression model and was found to be non-significant (OR = 1.01, p = 0.837). Therefore, it was not included in the final multivariable model.

Multivariable analysis confirmed residual small bowel length (p: 0.027) and weight Z score (p: 0.0061) to independently predict the response to treatment at 52 weeks (Fig. 3). In particular, a 10 cm increase in residual bowel is associated with a 33% increased probability of response while for each unit increase in weight z-score, the probability to respond increased by 82%. Multivariable analysis also confirmed that pre-treatment liver dysfunction was negatively associated with on one-year response (p: 0.010), reducing the likelihood of responding to TED by 82%.

Although the median values of oral intake (before treatment) were available for only 42 out of 104 patients, there was no statistically significant difference between responders and non-responders (1000.0 kcal, IQR 680.0–1563.0 vs. 950.0 kcal, IQR 500.0–1625.0, respectively, p = 0.48).

From the analysis of all biochemical factors' modification during the first six months of treatment we found that an early increase in mean haemoglobin level was associated with 1 year response to treatment (p: 0.070). Parallelly, no other significant difference was seen between responders or non-responders to TED treatment in particular for urea, urinary sodium (NaU), urinary potassium (KU) and the ratio between NaU/KU.

	Total	1-year response		p
	N = 104	No (N = 36)	Yes (N = 68)	
6-months response				
No	47 (45.2%)	32 (88.9%)	15 (22.1%)	<0.001[a]
Yes	57 (54.8%)	4 (11.1%)	53 (77.9%)	

[a]Significance level of p < 0.05.

Table 2: **Association between 6-months vs. 12 months clinical response.**

Early predictors of PN weaning

The potential effect of study center was tested in a logistic regression model and was found to had a borderline association with PN weaning (OR = 1.19, p = 0.050).

According to the univariate analysis, lower (PNDI) (p: 0.0020) lower volume (p: 0.017) and calories (p: 0.0071) of weekly PN and higher serum citrulline (p: 0.0083) predicted the possibility of weaning patients off PN support.

These variables were then included in a multivariable model that confirmed that pre-treatment calories <35 kcal/kg/day (p: 0.044) and citrulline ≥14 μmol/L before treatment (p: 0.047) were predictors of PN complete weaning (Fig. 4). Due to the small number of PN weaning events (N = 21), the center variable was not included in the multivariable model to avoid overfitting.

Similarly to predictors of response, no difference was observed between weaned and non-weaned patients according to enteral intake (1000.0 kcal, IQR 931.0–1880.0 vs. 1000.0 kcal, IQR 567.0–1490.0, p = 0.53).

Biochemical modification in the first 6 months was evaluated according to PN weaning in the first year of treatment.

Early and steady increases in mean Hb (p: 0.014) and citrulline levels (p: 0.044) in the first 6 months were associated to PN weaning (Figs. 5 and 6). In particular, from the ROC analysis, a relative increase of 2.8% in haemoglobin level at 6 months discriminated patients with PN weaning from those with no weaning with acceptable sensitivity (0.75) and specificity (0.62) while an optimal threshold for citrulline increase at 6 months was not identified. No other significant difference was found in biochemical parameters' modification according to PN weaning; in particular no changes in urea, NaU, KU and NaU/KU.

Supplementary Figure S1 shows the increasing trend in the probability of 1-year PN weaning with increasing relative changes in haemoglobin levels: for example, an increase in haemoglobin of 10% at 3 and 6 months was associated with a 1-year PN weaning probability of 22% and 25%, respectively; an increase in haemoglobin 30% at 3 and 6 months was associated with a 1-year PN weaning probability of 40% and 50%, respectively.

Adverse events

During the study period 27 of 104 patients (25.9%) experienced at least one adverse event (AE) after a median time of 4.5 months (IQR 1.1–7.1).

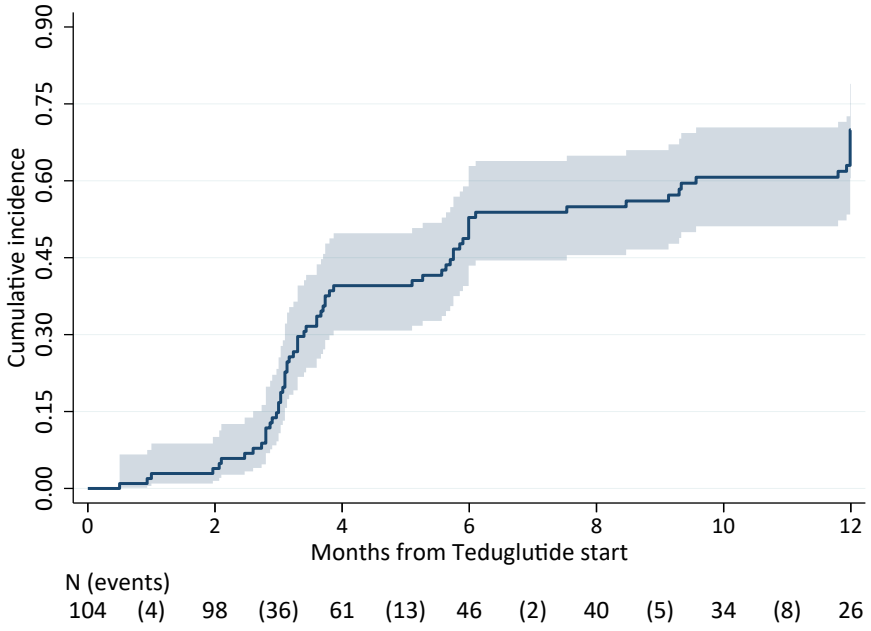

Fig. 1: **Time to 1-year response to TED defined as a reduction in PN volume/calories ≥20%**. The table below the x-axis shows the number of patients at risk (N) and the number of new events -responses- (in parentheses) at each time point. Response was achieved by 68 patients during the first year with 53 (78%) of them achieving it in the first 6 months.

Among a total of 33 adverse events, 16 (48%) were classified as serious. Seven out of the total serious adverse events were categorised as related to TED treatment, namely: intestinal sub obstruction (n = 3), occlusion (n = 2), heart failure due to left ventricular hypertrophy (n = 1), and catheter infection (n = 1).

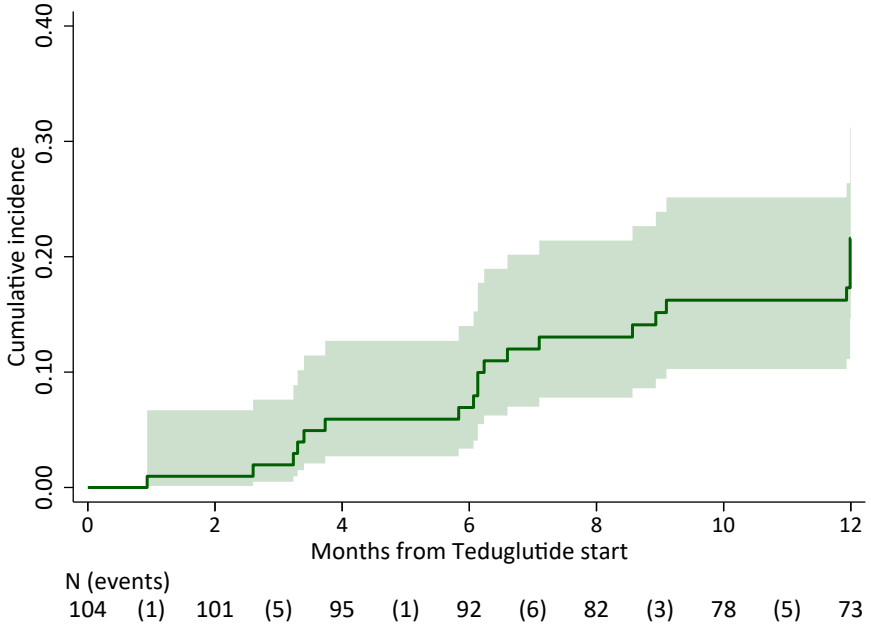

Fig. 2: **Time to 1-year PN weaning**. The table below the x-axis shows the number of patients at risk (N) and the number of new events -weaning- (in parentheses) at each time point. Complete PN weaning in the first year of treatment was achieved in 21 children (20.2%).

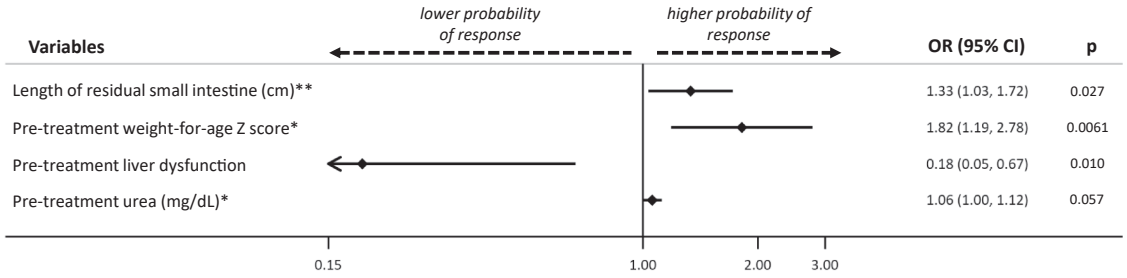

***Fig. 3:* Predictors of 1-year response obtained by a multivariable logistic regression model**. Legend. OR: Odds ratio; CI: Confidence interval; *For 1-unit increase; **For 10 cm increase. Estimates were obtained using a multivariable logistic regression model. Odds ratios (ORs) for 1-year response (diamonds) were plotted with 95% confidence intervals (CIs) (solid lines).

Endoscopy was performed early as per TED surveillance protocol without any finding. No other indirect sign of polyps arose during the study period.

Table 3 show the description of total AEs and serious adverse events (SAEs).

Discussion

This real-world study on TED treatment in children with SBS found that more than 60% of children achieved a clinical response, defined as a 20% or greater reduction of PN requirements; one-third of them achieved complete PN weaning during the first year of treatment. Children with a longer residual small bowel, better nutritional status, and absence of elevated liver enzyme at the start of treatment had a higher rate of response to TED. Lower PN calories requirements and higher citrulline levels before treatment start increased the probability of complete PN weaning. An increase in Hb and citrulline levels during the first 6 months of treatment predicted PN weaning following one year of TED treatment.

The response rate after 1 year of treatment was recently extrapolated from the pool analysis of the 3 TED clinical trials enrolling in total 78 children and was reported to be at 78.2%.[20] The PN weaning rate in the same group of patients was 19.2%. The results from our cohort showed a slightly lower response rate to TED treatment (60%); however, the rate of PN weaning was very similar (20%). It is important to acknowledge that the reduction of at least 20% of PN needs is significantly impacted by clinicians' subjectivity, and that within the three clinical trials more than 40% of children with SBS achieved the same reduction of PN without access to TED treatment. It is noteworthy that PN weaning is a more objective parameter and it is less affected by the different care provided to the patients. Furthermore, this real-life cohort had a shorter residual small intestine than the clinical trial cohort and allowed enrollment of patients with liver dysfunction.

The 48 weeks open label trial from France showed a very high response rate with 96% achieving at least a 20% reduction in PN and 32% of total PN weaning.[21]

Real-life experiences with more than 10 children from Israel and Spain demonstrated a range of response rate from 62% to 87% of 20% PN reduction and 15%–33% of complete PN weaning, reflecting a very high variability across different centers.[22,23]

Pretreatment predictors of response were analysed only in the pool analysis of clinical trials and revealed some similarities to our results, such as the length of the residual small bowel and lower PN requirements. However, those results did not distinguish between a simple response and a total PN weaning.

Our study showed for the first time that even mild elevated liver enzymes and lower weight z-score are

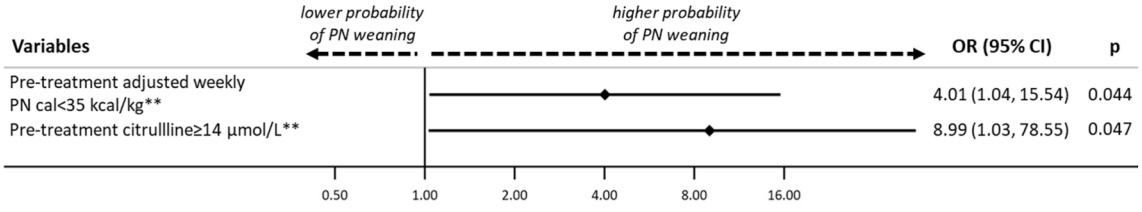

***Fig. 4:* Predictors of 1-year PN weaning estimated by a multivariable logistic regression model**. Legend: OR: Odds Ratio; CI: Confidence Interval; **Cutoff identified by the corresponding ROC curve. Estimates were obtained using a multivariable logistic regression model. Odds ratios (ORs) for 1-year PN weaning (diamonds) were plotted with 95% confidence intervals (CIs) (solid lines). Due to the small number of events and the quasi-complete separation in pretreatment citrulline ≥14 µmol/L, the resulting odds ratios may be unstable and associated with wide confidence intervals. This reflects model uncertainty and should be interpreted with caution.

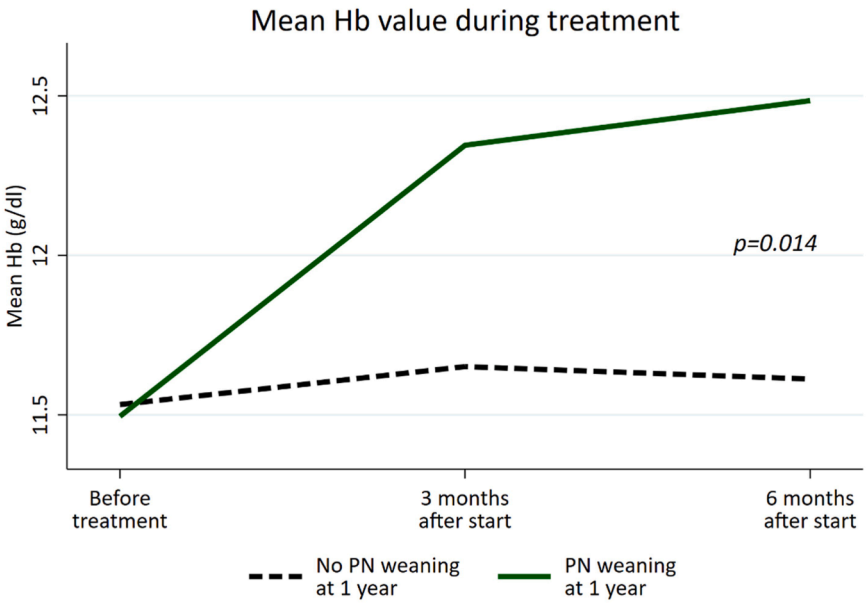

Fig. 5: **Trend of haemoglobin (Hb) values over time according to PN weaning**. Trends in haemoglobin (Hb) values during the first 6 months of Teduglutide therapy according to PN weaning at 1 year. A linear mixed-effects model was used to explore whether early changes in haemoglobin were different between patients weaned from PN compared to those not weaned. This model included group (PN weaning vs. no PN weaning), time and group–time interaction as fixed effects, and patient as random intercept (to account for patient variability). The p-value of 0.014 represents the p-value of the group–time interaction term, indicating that there is a significant interaction between PN weaning and time. This suggests that the two groups experienced different changes in Hb levels over time.

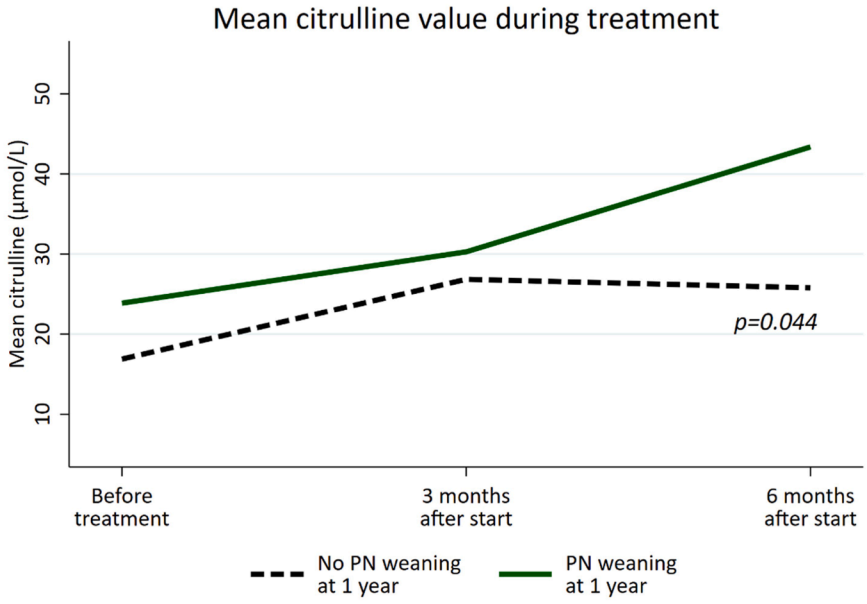

Fig. 6: **Trend of citrulline values over time according to PN weaning**. Trends in citrulline values during the first 6 months of Teduglutide therapy according to PN weaning at 1 year. A linear mixed-effects model was used to explore whether early changes in citrulline were different between patients weaned from PN compared to those not weaned. This model included group (PN weaning vs. no PN weaning), time and group–time interaction as fixed effects, and patient as random intercept (to account for patient variability). The p-value of 0.044 represents the p-value of the group–time interaction term, indicating that there is a significant interaction between PN weaning and time. This suggests that the two groups experienced different changes in citrulline levels over time. It should be noted that the 6-month citrulline values are only available for 41 and 43 patients, respectively.

	Adverse events (AEs)	
	Any grade	Grade III-IV
Total number of AEs	33	12
Type of AE		
Upper-respiratory-tract infection	5 (15.2%)	1 (8.3%)
Abdominal distension	3 (9.1%)	–
Abdominal pain	4 (12.1%)	–
Congestive heart failure	1 (3.0%)	–
Catheter related blood stream infections (CRBSI)	5 (15.2%)	5 (41.7%)
Other	15 (45.5%)	6 (50.0%)
Specify		
Anastomotic stricture	1 (6.7%)	1 (16.7%)
Catheter obstruction	1 (6.7%)	–
Constipation and abdominal distension	1 (6.7%)	–
D-lactic acidosis	1 (6.7%)	1 (16.7%)
Elevated liver enzymes	1 (6.7%)	–
Enteritis	1 (6.7%)	–
Exit site infection (tunnelitis)	1 (6.7%)	–
Intestinal sub-obstruction	3 (20.1%)	2 (33.4%)
Occlusion	2 (13.3%)	2 (33.4%)
Swollen and painful joints	1 (6.7%)	–
Transient generalized pruritus	1 (6.7%)	–
Vomiting	1 (6.7%)	–
Serious Adverse Events (SAEs)	16 (48.5%)	11 (91.7%)
Relation with teduglutide		
No	9 (56.3%)	
Yes	7 (43.8%)	
Specify		
Unlikely related	1 (14.3%)	
Possible related[a]	1 (14.3%)	
Probable related[b]	5 (71.4%)	

[a]There is a possibility that Teduglutide is the cause of the AE, but it is not the most likely explanation and there are other potential explanations.
[b]Teduglutide is more likely to be the cause of the AE than other explanations. There are strong indications to support this relationship.

Table 3: **Adverse Events (AEs) during 12 months of treatment with Teduglutide and relationship between serious adverse events (SAE) and treatment.**

predictors of lack of response to TED; the recognition of these predictors may be due to the real-life use of the drug, since in our protocol we had wide inclusion criteria. Indeed, in clinical trials, liver abnormalities represented an exclusion criterion for enrollment. By contrast, in preclinical study, the role of GLP-2 of modulation of liver function is still debated since two articles seem to suggest a protective role,[24,25] one a harmful role[26] and one an dose-mediated effect,[27] but none studied the impact of liver disfunction on response to TED treatment.

Another interest finding of this study is the utility of serum citrulline in identifying patients unlikely to respond to TED. We calculated that a cut-off of 14 μmol/L of citrulline before treatment distinguished children who achieved PN weaning after 12 months of TED. Of note, due to the small number of events, this result should be interpreted with caution.

The use of longitudinal markers to predict the response to TED treatment has not been explored previously. By prospectively enrolling one of the largest cohorts of patients with SBS on TED treatment, we were able to confirm that haemoglobin increase in the first 6 months is a valid marker of PN weaning. There are no previous studies linking TED to haemoglobin. The interpretation of this finding is twofold, possibly reflecting an improved absorptive capacity in iron and/or vitamin B12 of the residual bowel or the excessive hemoconcentration that follows aggressive weaning. A possible increase in intestinal absorption was further confirmed by the significant increase in citrulline in children who achieved PN weaning, which is consistent with a previous report on a smaller group of children by Lambe et al.[21] This hypothesis should be confirmed in future prospective studies. Furthermore, no significant difference was seen during the first 6 months of TED treatment in NaU/KU ratio stratified either by response or by PN weaning, making the hypothesis of hemoconcentration throughout dehydration less possible.

Based on the presented results, we may define the best candidate for fulfilling the goals of TED treatment. If the aim is a response to treatment during the first year, we should probably try to enroll patients with a higher weight z-score, longer residual small bowel and with normal liver function tests at enrollment. The aim of complete PN weaning can probably only be met by children with lower PN requirements and higher citrulline levels before treatment. This in strong accordance with results of real-life on French adults.[28] Monitoring their haemoglobin and citrulline increase from baseline to 6 months of treatment might be useful to decide if TED treatment should be continued.

The number and percentage of SAEs in our cohort was much lower than in the pooled analysis of clinical trials[29]; however, our SAE are more often judged to be related to TED treatment compared to the clinical trials. Moreover we did not find any sign on duodenal polyps in the first year of treatment as outlines in a recent adult publication.[30]

Our study has several limitations: due to the multicenter design no standardised protocol for PN reduction was applied in the different centers. However, it is important to note that all centers were tertiary referral centers for intestinal rehabilitation in Europe, which follows international guidelines for the correct management of SBS children. Moreover, our preliminary analysis showed no significant center effect on the probability of 1-year response. This supports the consistency of the results across centers. Although a borderline center effect was observed for PN weaning, the small number of events limited our ability to include this variable in the multivariable model. This

represents a limitation, but we believe it was a necessary methodological choice to preserve model validity.

In addition, without standardised protocol some data were missing such as regular monitoring of citrulline and oral intake or information on intravenous iron supplementation and blood transfusions. In addition being a big multicenter cohort did not allow us for further intestinal absorption exams as done in the French trial.[21] Furthermore, as stated earlier, PN reduction of $\geq$20% might be strongly affected by the clinician's decision; at the end, the most plausible parameter of TED efficacy probably remains complete PN weaning.

The strength of the current study is that it represents the largest cohort of patients with SBS treated with TED reported so far, and despite being a real-life study, the patients were closely monitores, allowing the collection of all relevant clinical and biochemical markers.

In conclusion, this real-life study of 104 children with SBS-IF treated with TED showed a response rate of 60% and PN weaning in 20% of children. The children with the highest citrulline levels and the least PN calories requirements at baseline had a higher probability to be weaned of PN. However, partial reduction of PN can also be beneficial for children with SBS-IF and was more likely to be observed in children with longest residual small bowel, highest weight z-score and normal liver enzymes at baseline. Before starting the treatment, all these parameters should be recorded and clear objectives should be given on the expected response and whether the treatment needs to be discontinued after a few months in case of non-response. This will increase cost-effectiveness of the TED use. The study defined also possible during treatment predictive parameters which should be explored for further confirmation, thus providing clearer indications for the use and withdrawal of TED in children with SBS.

Contributors

LN: conceptualisation, data curation, funding acquisition, investigation, methodology, resources, software, visualisation, writing—original draft, and writing review & editing.

AG: data curation, formal analysis, methodology, project administration, software, supervision, validation, writing review & editing.

ERB: data collection, methodology, writing review & editing.

AGM: data collection, methodology, writing review & editing.

IH: data collection, methodology, writing review & editing.

JH: data collection, methodology, writing review & editing.

IJB: data collection, methodology, writing review & editing.

RGS: data collection.

AL: data collection, methodology, writing review & editing.

PG: data collection.

PP: data collection.

CL: data collection, methodology, writing review & editing.

LD: funding acquisition, investigation, methodology, resources, writing review & editing.

LN, AG, and LD have access to and verify the underlying study data.

Data sharing statement

All statistical outputs in the present study are included in the main text or the Supplementary Files. Data, analytic methods, and study materials might be made available to other researchers upon specific request to the corresponding author. Aggregate results not present in the current study might be shared upon request and after agreement by all authors of the manuscript with no permission of publication.

Declaration of interests

LN, JH, IH has received consultant honoraria from Takeda but none related with this publication. CL has received consultant honoraria from VectivBio and Fresenius Kabi, unrelated related to the current publication, and served on an advisory board for VectivBio in 2023. The rest of authors have no conflicting interests related to this publication.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103343.

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