

British Intestinal Failure Alliance (BIFA) Position Statement

Use of peptide growth factors for adult patients with intestinal failure Authors: Siddhartha Oke, Jeremy Nightingale, Palle Jeppesen and the BIFA committee August 2018

Summary

There are many potential growth factors that help absorption in patients with a short bowel. Their main aim is to promote and often exceed the normal structural adaptive process after a small bowel resection. They may reduce the symptoms (less stomal output/diarrhoea) and help patients with a short bowel, reduce or stop the amount of parenteral support required while the treatment is given. Growth factors have the disadvantages of both being extremely expensive at present (though prices may reduce considerably in the future) and there is the fear that they may promote neoplasia (or increase the growth rate if neoplasia is already present).

Currently only teduglutide has UK marketing authorisation for the treatment of adult patients with a short bowel.

Aims

To recommend when a peptide growth factor may be considered in a patient with short bowel associated intestinal failure (SB-IF).

To outline the pre-treatment process and the monitoring required, including when treatment should be stopped.

This position paper will discuss the use of generic peptide growth factors then mention specific ones (particularly growth hormone and teduglutide), that have, or may in the future be used clinically.

Introduction

Maintenance, growth and repair of the intestinal mucosa are dependent upon many intra and extra luminal factors including peptide hormones. It is in the peptide hormones (which, amongst other actions, influence mucosal growth) that most clinical work has been performed. These hormones are often referred to as intestinal growth factors, though it is important to note that they often have other effects upon the gut (e.g. reducing secretions and gastrointestinal motility (e.g. glucagon like-peptide 1 (GLP-1)).

BAPEN brings together the strengths of its Core Groups to optimise nutritional care



*British Association for Parenteral and Enteral Nutrition Registered Charity 1023927

The aim in the management of SB-IF is to maximise residual intestinal function and provide supplementary fluid and/or nutrition so that patients achieve and maintain a healthy nutrition, water and electrolyte status.

The ideal outcome is for patients to have improvement in gastrointestinal symptoms e.g. reduction of high stoma output/diarrhoea, and stop all artificial nutritional support, though this is often not possible. Treatments to achieve this include oral fluid management, oral rehydration solutions, dietary modification, anti-secretory and anti-motility medications, growth factors and surgery.

There are now good trial data showing the potential benefit of some intestinal growth factors in patients with SB-IF¹. The growth factors may hasten or exceed the normal intestinal adaptation response (both structural and functional) that occurs with time, particularly in those with jejunum in continuity with a functioning colon (this rarely takes longer than 3 years). At least two hormones were postulated to stimulate adaptation in patients with a short bowel. These were Peptide YY (mainly slows motility) and glucagon like peptide-2 (GLP2) (mainly stimulates growth), both are produced by the enteroendocrine L cells in the terminal ileum and colon and both are found at low concentrations in the blood of patients with a jejunostomy and at very high concentrations after the colon is brought into continuity with the jejunum²⁻⁴. Amongst the other hormones GLP-1, GIP, oxyntomodulin are likely to be responsible for the clinical adaptation observed as patients gradually require less nutrition and fluid support with time.

The aims of peptide growth factors, or indeed any treatment for SB-IF, are to reduce the severity of the intestinal failure. Clinically this means maximising gut function and minimizing the gastrointestinal related symptoms associated with malabsorption, so that the amount of nutrition, water and electrolyte support given can be reduced. For those needing parenteral support this means reducing the volume, energy or electrolyte content of the feed, and/or allowing nights free from parenteral support or indeed even completely stopping parenteral support. In others with less severe intestinal failure it may mean stopping subcutaneous fluid infusions or oral/enteral nutrition or fluid support.

There is a commercially produced analogue of GLP-2 (teduglutide) that has undergone extensive clinical trials to show its efficacy, but a high cost has currently precluded its extensive use.

BAPEN brings together the strengths of its Core Groups to optimise nutritional care



*British Association for Parenteral and Enteral Nutrition Registered Charity 1023927

Recommendations

1. *In whom may peptide growth hormones be considered?*

Patients with a short bowel and dependent upon parenteral support and/or:

- a) Have had a functioning colon in continuity for at least a year to allow intestinal adaptation to occur. If no functioning colon is in circuit then adaptation will not occur and treatment can be considered sooner (at about 6 months) after the surgery that resulted in the jejunostomy.
- b) Have no defunctioned small or large bowel that can be brought into continuity. Patients who are candidates for surgical reconstruction should have this surgery before growth factor therapy is considered.
- c) Patients who have been stable on parenteral support for 1 year, with the volume, nutrient and electrolyte content of the parenteral support and oral intake being optimised prior to starting.
- d) A patient who, with therapy, may be able to stop parenteral support.
- e) Patients with an unmanageable high output (e.g. >4 litres/24 hours) and whose quality of life is poor.
- f) Patients who with treatment may be able to have nights off parenteral support (may include subcutaneous fluid).

2. *What are the aims of treatment?*

- a) To have a reduction in stomal output of more than 1.5 L/24 hrs.
- b) To stop or achieve more than 2 night off/week of parenteral support.
- c) To have an improved quality of life (QOL). It is those with highest stomal output who report the most significant improvement in QOL⁵

3. *What should be done before starting a peptide growth factor?*

- a) For patients with a residual colon, a colonoscopy should be performed to detect and remove colorectal polyps.
 - I. If no polyps are found on index colonoscopy, yearly colonoscopy / imaging of colon should be performed for first 2 years of treatment
 - II. If polyps are found on the index colonoscopy, polypectomy should be performed and patients should undergo follow-up polyp surveillance as per the national guidelines or at 1 year if within the first 2 years of treatment (whichever is the shorter interval).
- b) A baseline CT thorax, abdomen and pelvis may be performed before or within 3 months of starting treatment.
- c) Clear goals of therapy must be stated and also the criteria for stopping treatment.
- d) In patients with a history of cardiac failure or insufficiency an echocardiogram should be performed with cardiac assessment.

BAPEN brings together the strengths of its Core Groups to optimise nutritional care



*British Association for Parenteral and Enteral Nutrition Registered Charity 1023927

4. What are the risks of treatment?

- a) Injection site reactions; redness, itching, pain.
- b) Fluid retention; oedema, weight gain, potential cardiac decompensation.
- c) Protrusion of the stomal nipple and potential signs of obstruction leading to abdominal pain/ileus.
- d) Due to increased blood flow, blood congestion and mucosal growth, a stricture may become even narrower hence obstructive episodes may be more common.
- e) A neoplasm may increase its growth rate. Colonic polyps may grow faster.
- f) A risk of pancreatic and biliary complications
- g) Treatment is likely to be life-long.

5. When should a peptide growth factor not be used or stopped?

They are contraindicated in patients with active or suspected malignancies, and if there is a history of malignancy in the previous 5 years especially within the GI tract including the hepato-biliary system.

6. How should treatment be monitored?

Patients should be reviewed in a clinic at least every 3 months while on treatment and should initially have their weight reported to their nutrition support team weekly until stable. There may be a rapid weight increase necessitating a reduction in parenteral support volume (+/- energy). There may also be increased absorption of their medications (e.g. anticoagulants, hypoglycaemic drugs and sedatives). Those with a narrow therapeutic index need careful monitoring. At the clinic visit in addition to the usual assessments of nutrition, fluid, catheter condition and function, underlying disease, oral intake, life style, and medication etc.; specific questions should be asked to determine if obstructive episodes are occurring or if there are any biliary or pancreatic problems. If problems are detected discontinuation of the peptide growth factor should be considered. Quality of life should be measured using a validated quality of life tool (e.g. SBS-QOL⁶ in which a change of 18 points is significant or the PNIQ⁷).

BAPEN brings together the strengths of its Core Groups to optimise nutritional care



*British Association for Parenteral and Enteral Nutrition Registered Charity 1023927

7. When should the peptide growth factor be stopped?

- a) If a patient develops any malignancy
- b) If patients develop recurrent obstructive episodes requiring hospitalisation then stopping or occasionally reducing the dose of the peptide growth factor should be considered.
- c) If the treatment goals of reducing parenteral support are not achieved by 24 weeks.

8. Can a peptide growth factor be taken during pregnancy and lactation?

No data are available regarding pregnancy and thus peptide growth factors should be avoided during pregnancy and lactation.

9. Who can prescribe peptide growth factors?

The use of peptide growth factors in patients with short bowel should be limited to clinicians with significant experience in this area. This will vary in different healthcare settings but should be from specialist and high volume intestinal failure and home parenteral nutrition centres, ideally with multidisciplinary specialist clinics set up for the purpose.

Clinically authorised peptide growth factors

GLP-2 and analogues (Teduglutide)

Extensive international multi-centred studies have shown GLP-2 and then teduglutide (with its longer half-life) improve intestinal absorption of fluid and nutrients so that the long-term volume and energy of the parenteral nutrition can be reduced and has even allowed a few patients to completely stop parenteral nutrition⁸⁻¹¹. Teduglutide has been licenced for use in patients with SB-IF.

What does Teduglutide do?

Teduglutide has many physiological effects including up-regulating small bowel mucosal growth leading to an increase in intestinal absorption such that the volume and energy content of parenteral support can usually be reduced. Its benefit may be greatest in patients with no functioning colon in circuit (i.e. jejunostomy patients). Data about the length of time that the benefits of teduglutide persist after stopping are limited (a few weeks with a jejunostomy and longer if a colon in continuity, up to 12 months)^{12,13}. Thus the drug needs to be continued to maintain a beneficial effect.

BAPEN brings together the strengths of its Core Groups to optimise nutritional care



*British Association for Parenteral and Enteral Nutrition Registered Charity 1023927

How is teduglutide given?

Once daily subcutaneous injection of 0.05mg/kg daily.

What is the cost of treatment?

Absolute costs may vary in different healthcare settings. As of 2018, the UK drug cost per quality adjusted life year is £193,549. This compares to a maximum cost of £85,775 per year for home parenteral support alone. However, this basic comparison is not a true reflection of cost. Complex cost benefit models are being taken into account any reduction in complications from being on HPN as well as the benefit on quality of life. At present a NICE appraisal is in process to gauge these issues.

Other growth factor treatments (not currently authorised for use)

Growth hormone

Growth hormone in combination with glutamine and a modified diet appeared to be beneficial^{14,15}. However subsequent randomised controlled studies showed no difference in the nutritional status of those patients treated with growth hormone together with glutamine and dietary modification compared to controls. This lack of efficacy was independent of the supra-physiological dosage that was given (lowest dose 0.024mg/kg/day, highest dose of 0.14mg/kg/day) and noted side effects included arthralgia and oedema¹⁶⁻²²(See appendix 1) .

Current View

Low 0.024 mg/kg/day and high dose 0.14 mg/kg/day growth hormone are not currently recommended as a treatment for adults with SB-IF from any cause or with any residual anatomy.

GLP-1 agonists and derivatives

Early clinical trial data for subcutaneous GLP-1 agonists and derivatives (e.g. exenatide and liraglutide) have shown some benefit in reducing stomal output and improving nutritional status in patients with short bowel^{23,24}, but longer term data from studies with a more robust design are not yet available.

Combination GLP-1 and GLP-2

The combination of GLP-1 and GLP-2 has only been assessed in one clinical trial²⁵ and suggested an improvement in hydration and increased fat mass in patients though this was a very small study with marked variability in small bowel length.

BAPEN brings together the strengths of its Core Groups to optimise nutritional care



*British Association for Parenteral and Enteral Nutrition Registered Charity 1023927

Epidermal growth factor (EGF)

EGF is a natural intraluminal repair peptide produced in saliva and the Brunner's glands in the duodenum. It plays a role in intestinal adaptation after massive small bowel resection^{26,27,28} in murine models. Treatment with exogenous EGF following a small bowel resection has been shown to increase small bowel villous height, crypt depth, and bowel length, as well as increasing overall animal weight^{29,30}.

There has been one clinical pilot study of 6 weeks of 5 children (1-2 months after their index surgery causing a short bowel) given 100 microgram/kg of recombinant human EGF/day. There was an improvement in carbohydrate absorption. This study was limited by a lack of long term follow up of all but one patient³¹.

Insulin-like growth factor 1 (IGF-1)

IGF-1 is a 70 amino acid polypeptide primarily produced by the liver, with some additional synthesis taking place in the intestine, where its secretion is regulated by growth hormone, insulin, and intraluminal nutritional intake³². IGF has been demonstrated to increase epithelial growth and crypt expansion³³.

To date, no clinical trials have investigated the therapeutic administration of IGF-1 to humans with short bowel.

Summary

Peptide analogues of endogenous hormones are being developed and will have a use in patients with a short bowel. Currently only teduglutide is available in the UK. If funding is approved it may be clinically useful to help patients with a short bowel stop or reduce the amount of parenteral support required.

Notes

1. In the US teduglutide is sold under the trade name of Gattex® and is licenced by the Food and Drug Administration (FDA), while in the UK and Europe it is sold under the trade name of Revestive®
2. There are differences between the prescribing information for Gattex® in the USA (http://www.shirecontent.com/PI/PDFS/Gattex_USA_ENG.pdf) and Revestive® in the UK (<http://www.medicines.org.uk/emc/medicine/29315>). The statements below will give the consensus position of the BIFA committee.

BAPEN brings together the strengths of its Core Groups to optimise nutritional care



*British Association for Parenteral and Enteral Nutrition Registered Charity 1023927

Appendix 1

Table to illustrate the Growth Hormone Studies



Putting patients at the centre
of good nutritional care

Registered Charity No.1023927

Factor	Drug	Author	Year	Trial type	Patient numbers	Duration of trial	Patient group	End point(s) measured	Summary outcomes
Growth Hormone	Growth hormone + glutamine + diet modification	Byrne ¹⁴	1995	Non randomised retrospective cohort	10	4 week	SB	Improvement in absorption	
	Growth Hormone + glutamine + diet modification	Byrne ¹⁵	1995	Non randomised prospective cohort study + extension study	15	4 weeks	SB	Improvement in absorption	Combined growth hormone + glutamine + modified diet enhanced nutrient absorption
	Growth Hormone + glutamine + diet modification	Byrne ¹⁵	1995	Non randomised prospective cohort study	47	4 weeks (1 year follow up)	SB	Bowel rehabilitation with long term reduction in PS support	Growth hormone + diet + glutamine increased protein absorption p<0.02 and reduced stool output p<0.05
	Growth Hormone + glutamine + low fat high carbohydrate diet	Scolapio ^{16,17}	1997	Randomised double blind placebo controlled cross over study	8	6 week	SB	Micronutrient absorption, small intestinal morphology, gastric emptying, stoma output	1 year FU showed 40% of patients were able to be maintained of PS and 40% of patients had reduction in PS.
	Growth Hormone	Ellegard ²²	1997	Randomised double blind placebo controlled cross over study	10	8 weeks	SB	Lean body mass increase	No difference in small intestinal morphology and no increase in micronutrient absorption. Some decrease in gastric emptying p=0.008 and in stoma output p=0.03
	Growth hormone + glutamine	Szkudlarek ¹⁸	2000	Randomised double blind placebo controlled cross over study	8	56 days (28 days each arm)	SB	Improvement in intestinal absorption	5% Increase in lean body mass p<0.05
	Growth hormone	Seguy ¹⁹	2003	Randomised double blind placebo controlled cross over study	12	7 weeks (3 weeks each arm with 1 week washout)	SB	Improvement in intestinal absorption	No improvement in intestinal absorption
	Growth hormone + glutamine + diet modification	Byrne ²¹	2005	Randomised double blind placebo controlled study	41	6 weeks + 3 month follow up	SB	Decrease in PS requirements	Low dose growth hormone increase intestinal absorption.
									Growth hormone and glutamine with dietary changes decrease PS requirements (p<0.005)

BAPEN brings together the strengths of its Core Groups to optimise nutritional care



*British Association for Parenteral and Enteral Nutrition Registered Charity 1023927

References

1. Oke S, Walter MNM, Ansari T, Gabe SM. Growth factors and their use in short bowel. *Curr Opin Gastroenterol.* 2017;33(3):212-217.
2. Nightingale JM, Kamm MA, van der Sijp JR, Ghatei MA, Bloom SR, Lennard-Jones JE. Gastrointestinal hormones in short bowel syndrome. Peptide YY may be the “colonic brake” to gastric emptying. *Gut.* 1996;39(2):267-272.
3. Jeppesen PB, Hartmann B, Thulesen J, et al. Elevated plasma glucagon-like peptide 1 and 2 concentrations in ileum resected short bowel patients with a preserved colon. *Gut.* 2000;47(3):370-376.
4. Jeppesen PB, Hartmann B, Hansen BS, Thulesen J, Holst JJ, Mortensen PB. Impaired meal stimulated glucagon-like peptide 2 response in ileal resected short bowel patients with intestinal failure. *Gut.* 1999;45(4):559-563.
5. Jeppesen PB, Pertkiewicz M, Forbes A, et al. Quality of life in patients with short bowel syndrome treated with the new glucagon-like peptide-2 analogue teduglutide – Analyses from a randomised, placebo-controlled study. *Clin Nutr.* 2013;32(5):713-721.
6. Berghöfer P, Fragkos KC, Baxter JP, et al. Development and validation of the disease-specific Short Bowel Syndrome-Quality of Life (SBS-QoL™) scale. *Clin Nutr.* 2013;32(5):789-796.
7. Wilburn J, McKenna SP, Heaney A, et al. Development and validation of the Parenteral Nutrition Impact Questionnaire (PNIQ), a patient-centric outcome measure for Home Parenteral Nutrition. *Clin Nutr.* 2018;37(3):978-983.
8. Jeppesen PB, Gilroy R, Pertkiewicz M, Allard JP, Messing B, O’keefe SJ. Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome. *Gut.* 2011;60(7):902-914.
9. O’Keefe SJD, Jeppesen PB, Gilroy R, Pertkiewicz M, Allard JP, Messing B. Safety and Efficacy of Teduglutide After 52 Weeks of Treatment in Patients With Short Bowel Intestinal Failure. *Clin Gastroenterol Hepatol.* 2013;11(7):815-823.e3.

BAPEN brings together the strengths of its Core Groups to optimise nutritional care



*British Association for Parenteral and Enteral Nutrition Registered Charity 1023927

10. Jeppesen PB, Pertkiewicz M, Messing B, et al. Teduglutide Reduces Need for Parenteral Support Among Patients With Short Bowel Syndrome With Intestinal Failure. *Gastroenterology*. 2012;143(6):1473-1481.e3.
11. Schwartz LK, O’Keefe SJD, Fujioka K, et al. Long-Term Teduglutide for the Treatment of Patients With Intestinal Failure Associated With Short Bowel Syndrome. *Clin Transl Gastroenterol*. 2016;7(2):e142.
12. Compher C, Gilroy R, Pertkiewicz M, et al. Maintenance of Parenteral Nutrition Volume Reduction, Without Weight Loss, After Stopping Teduglutide in a Subset of Patients With Short Bowel Syndrome. *J Parenter Enter Nutr*. 2011;35(5):603-609.
13. Jeppesen PB, Lund P, Gottschalck IB, et al. Short bowel patients treated for two years with glucagon-like peptide 2: Effects on intestinal morphology and absorption, renal function, bone and body composition, and muscle function. *Gastroenterol Res Pract*. vol 2009 Article ID 616054, 12 pages.
14. Byrne TA, Morrissey TB, Nattakom T V, Ziegler TR, Wilmore DW. Growth hormone, glutamine, and a modified diet enhance nutrient absorption in patients with severe short bowel syndrome. *JPEN J Parenter Enteral Nutr*. 19(4):296-302.
15. Byrne TA, Persinger RL, Young LS, Ziegler TR, Wilmore DW. A new treatment for patients with short-bowel syndrome. Growth hormone, glutamine, and a modified diet. *Ann Surg*. 1995;222(3):243-54; discussion 254-5.
16. Scolapio J, Camilleri M, Fleming C, et al. Effect of growth hormone, glutamine, and diet on adaptation in short- bowel syndrome: A randomized, controlled study. *Gastroenterology*. 1997;113(4):1074-1081. doi:10.1053/gast.1997.v113.pm9322500.
17. Scolapio JS. Effect of growth hormone, glutamine, and diet on body composition in short bowel syndrome: a randomized, controlled study. *JPEN J Parenter Enteral Nutr*. 23(6):309-12; discussion 312-3.
18. Szkudlarek J, Jeppesen PB, Mortensen PB. Effect of high dose growth hormone with glutamine and no change in diet on intestinal absorption in short bowel patients: a randomised, double blind, crossover, placebo controlled study. *Gut*. 2000;47(2):199-205.

BAPEN brings together the strengths of its Core Groups to optimise nutritional care



*British Association for Parenteral and Enteral Nutrition Registered Charity 1023927

19. Seguy D, Vahedi K, Kapel N, Souberbielle J, Messing B. Low-dose growth hormone in adult home parenteral nutrition-dependent short bowel syndrome patients: A positive study. *Gastroenterology*. 2003;124(2):293-302.
20. Seguy D, Vahedi K, Kapel N, Souberbielle J-C, Messing B. Low-dose growth hormone in adult home parenteral nutrition-dependent short bowel syndrome patients: a positive study. *Gastroenterology*. 2003;124(2):293-302.
21. Byrne TA, Wilmore DW, Iyer K, et al. Growth Hormone, Glutamine, and an Optimal Diet Reduces Parenteral Nutrition in Patients With Short Bowel Syndrome. *Ann Surg*. 2005;242(5):655-661.
22. Ellegård L, Bosaeus I, Nordgren S, Bengtsson BA. Low-dose recombinant human growth hormone increases body weight and lean body mass in patients with short bowel syndrome. *Ann Surg*. 1997;225(1):88-96.
23. Kunkel D, Basseri B, Low K, et al. Efficacy of the glucagon-like peptide-1 agonist exenatide in the treatment of short bowel syndrome. *Neurogastroenterol Motil*. 2011;23(8):739-e328.
24. Hvistendahl M, Brandt CF, Tribler S, et al. Effect of Liraglutide Treatment on Jejunostomy Output in Patients With Short Bowel Syndrome: An Open-Label Pilot Study. *JPEN J Parenter Enteral Nutr*. October 2016:014860711667226.
25. Madsen KB, Askov-Hansen C, Naimi RM, et al. Acute effects of continuous infusions of glucagon-like peptide (GLP)-1, GLP-2 and the combination (GLP-1+GLP-2) on intestinal absorption in short bowel syndrome (SBS) patients. A placebo-controlled study. *Regul Pept*. 2013;184:30-39.
26. Helmrath MA, VanderKolk WE, Can G, Erwin CR, Warner BW. Intestinal adaptation following massive small bowel resection in the mouse. *J Am Coll Surg*. 1996;183(5):441-449.
27. Shin CE, Helmrath MA, Falcone RA, et al. Epidermal Growth Factor Augments Adaptation Following Small Bowel Resection: Optimal Dosage, Route, and Timing of Administration. *J Surg Res*. 1998;77(1):11-16.

BAPEN brings together the strengths of its Core Groups to optimise nutritional care



*British Association for Parenteral and Enteral Nutrition Registered Charity 1023927



Putting patients at the centre
of good nutritional care

Registered Charity No.1023927

28. O'Brien DP, Nelson LA, Williams JL, Kemp CJ, Erwin CR, Warner BW. Selective Inhibition of the Epidermal Growth Factor Receptor Impairs Intestinal Adaptation after Small Bowel Resection. *J Surg Res.* 2002;105(1):25-30..
29. Iskit SH, Tugtepe H, Ayyildiz SH, Kotiloglu E, Dagli TE, Yeğen BC. Epidermal growth factor and bombesin act synergistically to support intestinal adaptation in rats with massive small bowel resection. *Pediatr Surg Int.* 2005;21(6):436-440.
30. Chaet MS, Arya G, Ziegler MM, Warner BW. Epidermal growth factor enhances intestinal adaptation after massive small bowel resection. *J Pediatr Surg.* 1994;29(8):1035-1039.
31. Sigalet DL, Martin GR, Butzner JD, et al. A pilot study of the use of epidermal growth factor in pediatric short bowel syndrome. *J Pediatr Surg.* 2005;40(5):763-768.
doi:10.1016/j.jpedsurg.2005.01.038.
32. Kuemmerle JF. Insulin-Like Growth Factors in the Gastrointestinal Tract and Liver. *Endocrinol Metab Clin North Am.* 2012;41(2):409-423.
33. Van Landeghem L, Santoro MA, Mah AT, et al. IGF1 stimulates crypt expansion via differential activation of 2 intestinal stem cell populations. *FASEB J.* 2015;29(7):2828-2842.

BAPEN brings together the strengths of its Core Groups to optimise nutritional care



*British Association for Parenteral and Enteral Nutrition Registered Charity 1023927