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British Intestinal Failure Alliance (BIFA) Position Statement

Use of GLP-2 analogues and other growth factors for adult patients with intestinal failure

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** competing interests:

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Summary

There are potential hormonal pro-adaptive factors that may help absorption in patients with a short bowel, including growth hormone and glucagon-like peptide-2 analogies. 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 (PS) required while the hormonal pro-adaptive factor is given. Data supporting the use of GH in adults is limited, and it may cause side effects. In contrast, several clinical trials have shown GLP-2 analogue therapy to be effective and well tolerated in patients with Intestinal failure resultant from a short bowel (SBS-IF). In 2022, the first GLP-2 analogue, Teduglutide, received approval by NICE as an option for treating SBS-IF in people over a year old [1]. Other GLP-2 analogues, Apraglutide and glepaglutide, remain under evaluation in clinical trials. Hormonal pro-adaptive factors are expensive and there is the fear that they may promote neoplasia (or increase the growth rate if neoplasia is already present).

Aims

While other hormonal pro-adaptive factors are mentioned, this position statement will concentrate on GLP-2 analogues which are (e.g., teduglutide) or are likely to become commercially available (apraglutide and glepaglutide).

- To recommend when GLP-2 analogue therapy may be considered in an adult with a short bowel associated intestinal failure (SBS-IF).
- To outline the pre-treatment process and the monitoring required, including when treatment should be stopped.

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 entero-hormones (some of which, amongst other actions, influence mucosal growth) that most clinical work has been performed. These hormones are often referred to as intestinal growth factors or better hormonal pro-adaptive 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)).

The aim in the management of SBS-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. This should result in an improvement in gastrointestinal symptoms (e.g., reduction of high stoma output/diarrhoea), and to reducing/stopping all clinically assisted nutrition and hydration. 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 entero-hormones in patients with SBS-IF [2]. The entero-hormones 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 (GLP-2) (mainly stimulates growth, decelerates the rapid transit and alleviates hypersecretions), 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 jejunum [3-5]. Amongst the other hormones GLP-1, GIP (gastric inhibitory peptide), oxyntomodulin are likely to be responsible for the clinical adaptation observed, as patients gradually require less nutrition and fluid support with time.

Entero-hormonal therapy aims to reduce the severity of intestinal failure. Clinically, for those needing parenteral support, this means reducing the volume, energy, or electrolyte content of the feed, and/or allowing nights free from PS or indeed even completely stopping PS. In others with less severe intestinal failure, it may mean stopping subcutaneous fluid infusions.

A commercially produced analogue of GLP-2 (teduglutide) has undergone extensive clinical trials to show its efficacy, and was approved by Scottish Medicines Consortium in 2020 and NICE in 2022 for patients over 1 year old [1,6]

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Recommendations

1. In whom may GLP-2 analogue therapies be considered? Patients with a short bowel, who are dependent upon PS 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) Have been stable on PS for 6 months to 1 year, with the volume, nutrient and electrolyte content of the PS and oral intake having been optimised. Patients' fluid balance should be considered optimised with standard SB therapies and dietary approaches before considering entero-hormonal therapy.

d) A patient who, with therapy, may be able to stop PS. (e.g., having 2 nights/week PS)

e) Patients with an unmanageable high output and whose quality of life is poor.

f) Patients who with treatment may be able to have nights off PS (e.g., having 2L PS each night).

2. Which patient groups are likely to benefit the most?

a) Patients who are not having PS every day or who have low weekly volumes of PS.

b) Patients with a jejunostomy, high PS requirements and high stomal losses despite an optimised short bowel regime.

c) Patients who have a good oral intake and do not experience recurrent obstructive symptoms when increasing their oral intake.

3. 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 one or more nights off/week of PS or a reduction in PS of more than 20%.

c) To have an improved quality of life (QOL). It is those with highest stomal output who report the most significant improvement in QOL [7]

d) Prevent the need for a small bowel transplant.

4. What should be done before starting* GLP-2 analogue therapy*?

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 within 3 months prior to starting treatment to exclude malignancy.

c) Clear goals of therapy must be stated and include the criteria for stopping treatment.

d) In patients with a history of cardiac failure or insufficiency an echocardiogram should be performed with cardiac assessment.

e) Crohn's disease should be quiescent; any active Crohn's should be treated with standard therapies in the first instance.

5. 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.

6. When should a GLP-2 analogue not be used or stopped?

a) Active or suspected malignancy of the gastrointestinal tract (including hepatobiliary system and pancreas) within the last 5 years.

b) Although there is no data in humans (no harmful effects have occurred in animals), it is advised not to take during pregnancy or breast feeding.

7. How should treatment be monitored?

Patients should be reviewed in a clinic frequently after starting therapy and then, when stable, at least every 3 months while on treatment.

There may be a rapid increase in absorption necessitating a reduction in PS volume (+/- energy). There may also be increased absorption of medications (e.g., anticoagulants, hypoglycaemic drugs, and sedatives). Those medications with a narrow therapeutic index need careful monitoring.

At the clinic visit 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 or the PNIQ [8,9]).

8. When should the GLP-2 analogue be stopped?

a) If a patient develops any malignancy.

b) If patients develop recurrent obstructive episodes requiring hospitalisation.

c) If the treatment goals of reducing PS by 20% are not achieved after 6 months.

9. Can a GLP-2 analogue *be taken during pregnancy and lactation?*

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

10. Who can prescribe GLP-2 analogue therapy?

The use of peptide pro-adaptive 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 integrated intestinal failure and home parenteral nutrition centres, ideally with multidisciplinary specialist clinics set up for the purpose.

Clinically authorised GLP-2 analogue therapies

GLP-2 and analogues (teduglutide, apraglutide and glepaglutide). 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 nutrition 10-13. Teduglutide has been licenced for use in patients with SBS-IF. Apraglutide and Glepaglutide are undergoing clinical trials and are not yet approved

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1. What does Teduglutide do?

Teduglutide has many physiological effects including up-regulating small bowel mucosal growth leading to an increase in intestinal absorption. In addition, teduglutide (like all GLP-12 agonists) also inhibits gastric hyper-secretion, slows the accelerated gastric emptying, stimulates intestinal (and portal) blood flow, and increases intestinal barrier function. All this usually leads to a reduction in the volume and energy content of PS.

Data about the length of time that 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) [14,15]. Thus the drug needs to be continued to maintain a beneficial effect.

2. How is teduglutide given?

Once daily subcutaneous injection of 0.05mg/kg daily.

3. What is the cost of treatment?

The list price of teduglutide is £521.98 for 5mg and £260.99 for 1.25mg (excluding VAT). However, there is a commercial arrangement for the NHS making teduglutide available to the NHS with a discount. The size of the discount is commercial in confidence. To avoid waste patients may have injections in a unit treating several patients at the same time.

Other peptide pro-adaptive factor treatments (not currently authorised for use)

Growth hormone

Growth hormone in combination with glutamine and a modified diet appeared to be beneficial[16,17.] 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 oedema [18-24.] 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., exenetide and liraglutide) have shown some benefit in reducing stomal output and improving nutritional status in patients with short bowel [25,26], 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 trial [27] 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.

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 a massive, small bowel resection [27-29] 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 [28-31].

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 patient [32].

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 expansion[33,34].

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

Although a PYY analogue (PYY slows motility and is probably responsible for functional adaptation in SB-colon patients) would appear a logical treatment, no analogues have been tested in humans.

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 PS required.

Notes

1. In the US teduglutide is sold under the trade name of Gattex® and is licenced by the Food and Drug Administation (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).

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