Use of peptide growth factors for adult patients with intestinal failure
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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))).
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-IF. 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 jejunum. 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.
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 if 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 QOL.

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.
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-QOL in which a change of 18 points is significant or the PNIQ°).
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 nutrition \(^8\text{-}^{11}\). 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) \(^12\text{-}^{13}\). Thus the drug needs to be continued to maintain a beneficial effect.
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\textsuperscript{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 oedema\textsuperscript{16–22} (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. exenetide and liraglutide) have shown some benefit in reducing stomal output and improving nutritional status in patients with short bowel\textsuperscript{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 trial\textsuperscript{25} 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 massive small bowel resection\textsuperscript{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\textsuperscript{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 patient\textsuperscript{31}.

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 intake\textsuperscript{32}. IGF has been demonstrated to increase epithelial growth and crypt expansion\textsuperscript{33}.

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.
### Appendix 1

#### Table to illustrate the Growth Hormone Studies

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


