**Glucagon-like peptide 2 analogues in the treatment of intestinal failure: a qualitative exploration of the views of patients and their families in decision making.**

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Abstract:

*Background and aims*

Patients with short bowel syndrome and type 3 intestinal failure (SBS-IF) are dependent on parenteral nutrition (PN), a lifesaving treatment but inconvenient and with risks. Glucagon-like peptide 2 analogue (teduglutide) can reduce patients’ need for PN. However, it comes with the risk of a number of side effects. This qualitative study investigated patients’ decision making process to start teduglutide and how family members contributed to the decision.

*Methods*

In-depth semi-structured interviews were conducted with nine participants, six patients with SBS-IF and three family members about the decision to take teduglutide. Interviews were transcribed verbatim and analysed using framework analysis.

*Results*

The prominent motivation for taking teduglutide (Revestive® Takeda Pharmaceuticals Limited) was reducing or stopping PN. Other motivations were to help others by assisting in developing the knowledge base around teduglutide, patients felt that they had nothing to lose by trying the drug and the support of relatives. The reasons patients considered not taking the drug were that they had accepted being on PN, the potential side effects of teduglutide and undergoing extra monitoring. However, the monitoring programme also acted as a motivator providing reassurance that patients would be observed and supported with side effects. Family members were happy to support patients’ decision to try teduglutide, although they had more reservations, indicating a higher risk threshold.

*Conclusion*

Patients considered potential benefits of teduglutide outweighed any disadvantages. Relatives, although supportive, had more reservations.

**Keywords**: short bowel syndrome, parenteral nutrition, Glucagon-like peptide 2, teduglutide, qualitative, patient experience

Introduction

Patients with type 3 intestinal failure (IF) are dependent on parenteral support which may include fluids, electrolytes and nutrients given via a central venous catheter (1). IF caused by short bowel syndrome (SBS-IF) is the most prevalent indication for receiving parenteral nutrition (PN) in Europe (2, 3). Although PN is recognised as a lifesaving therapy for these patients, it is not without risks. The complications of PN can be serious and include catheter related blood stream infections leading to bacteraemia and even septicaemia, and central venous thrombosis (4). There are also more long-term adverse effects of IF including hepatic failure and osteoporosis (5).

Moreover, it is well documented that PN is burdensome and patients who require PN have a decreased quality of life (QoL) (6-9). People dependent on PN are less likely to have full-time employment and may suffer from psychological problems such as depression and anxiety (6, 10). In addition, it has been found that those receiving PN have a decreased QoL compared to the general population due to physical problems (11, 12). PN also seems to have a dose related effect, with patients who have a greater number of infusions experiencing poorer QoL than patients receiving fewer infusions (13-15).

Glucagon-like peptide 2 (GLP-2) analogue (teduglutide) (16), is a promising therapy for patients with SBS-IF. It enhances electrolyte and nutrient absorption, which can reduce the volume and number of nights of PN that patients with SBS-IF require (17, 18). However, teduglutide is not without side effects such as abdominal pain, headaches and a possible increased risk of gastrointestinal cancer (19). Moreover, there has been little exploration of patient attitudes towards, taking the drug. The decision by patients to try teduglutide may not be straightforward. One study using questionnaires investigated patient QoL whilst on teduglutide and found it improved over the 24 week study period (20). It was suggested that this improvement was related to a reduction in PN volume but there was no significant difference in QoL between the teduglutide and placebo groups; although this could have related to the short duration of the study or the tool used to measure QoL (20). However, there is a paucity of data from qualitative interviewing where patients can freely express their views. The current study uses qualitative interviewing to investigate the reasons for patients’ decision making surrounding treatment options and how family members influence this process. This information would be helpful to clinicians wanting to initiate GLP-2 into treatment pathways for patients with SBS-IF.

Methods

Participants

Patients with SBS-IF receiving home PN under the care of an IF unit in the UK from September 2019 to February 2020 were invited to participate either by a research nurse or a member of the clinical team. The inclusion criteria were patients who had received PN for a minimum of 1 year postsurgical resection (to allow for gastrointestinal adaptation), were dependent on receiving PN at least twice a week, were able to inject themselves with teduglutide and had consented to take teduglutide. Patients were asked to nominate a family member who lived with them or who was involved in their home PN to participate. The study received ethical approval from East of England - Cambridgeshire and Hertfordshire Research Ethics Committee, 19/EE/0062 and all participants gave written informed consent. Patient consent was taken by a member of the medical team and family member consent by AMS.

Data collection

All participants took part in semi-structured interviews conducted either at their home or at hospital according to their preference. The patients and family members were interviewed separately, apart from a 10 minute section of one patient interview. Interview guides were developed for patients and family members via literature review and discussion between AMS, SB and JG; see supplementary material. All interviews were conducted by one researcher (AMS). AMS is an experienced qualitative researcher working at the University of Manchester (9, 21-24). She is not a member of the clinical team and had no prior relationship with the participants. The interview guide was used flexibly so that themes raised by the interviewee could be explored. Interviews lasted between 30-60 minutes and were recorded on an encrypted digital recorder. Interviews were transcribed verbatim using a transcription service. The accuracy of the transcription was checked from the recording by AMS.

Data analysis

Interview transcripts were managed using NVivo 12 and were analysed using framework analysis (25). This involves a five step process; familiarisation, identifying a thematic framework, indexing, charting, mapping and interpretation. The interview transcripts were repeatedly read by AMS to become familiar with them. A thematic framework was developed inductively from themes arising from the interview transcripts and also from the interview guide by AMS; the framework analysis can be used flexibly to generate themes both inductively from the data and deductively from interview guides (26). The framework was modified following discussion with JG. The framework was used by AMS to index the transcripts. Thematic charts were created by AMS. Coding and thematic charts were discussed and agreed between AMS and JG. Mapping and interpretation of the data as a whole was then undertaken by AMS, JG and SB. Quotations are used to illustrate the themes which are only noted as coming from a patient or family member to preserve patient confidentiality

Rigour was introduced by having two authors (AMS and JG) discuss and agree the coding framework. In addition, AMS kept field notes and a reflective diary.

**Results**

Of 16 patients invited to participate; six patients and three of their family members agreed to take part. Patients were on PN for between 2-7 nights per week; other baseline characteristics can be seen in table 1. Patients had various reasons for and against taking teduglutide (see figure 1). Their main motivation for taking teduglutide was to reduce or stop PN. They had multiple drivers for this, some were of physical origin and others were psychological sequalae. Overall, however, the patients felt they had nothing to lose by trying the drug and relatives were largely supportive of their decision. Although all patients thought about the side effects and monitoring involved in taking the drug, they considered that it was worth it.

**Table 1. Patient baseline characteristics and relationship of family member taking part**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Patients | Age1 | Underlying disease | Stoma | Years on PN1 | Number nights/week | Volume (ml) PN/week | Relative |
| Patient1 | 60-70 | Crohn’s | Yes | 5-10 | 7 | 14000 |  |
| Patient2 | 50-60 | Crohn’s | Yes | 15-20 | 7 | 24500 | Husband |
| Pateint3 | 50-60 | Crohn’s | No | 15-20 | 3 | 7730 | Son |
| Patient4 | 50-60 | Ischaemia | Yes | <5 | 7 | 24500 | Partner |
| Patient5 | 40-50 | Previous GI surgery | No | <5 | 2 | 4000 |  |
| Patient6 | 60-70 | Crohn’s | Yes | 5-10 | 5 | 10000 |  |

PN – parenteral nutrition GI – gastrointestinal 1Ranges are used for patient ages and years on PN to preserve patient confidentality.

*Reasons for taking teduglutide*

Reducing parenteral nutrition

The prominent reason for taking teduglutide was reducing or stopping PN. Patients described time constraints, psychological sequelae and their long term health as motivations for this.

All patients described the time constraints associated with PN. They could be attached to a machine for 12 hours up to seven days per week; reducing the time on PN would give them more opportunity for other activities. “If I’m not on my machine for that night…then I could plan to do something. That could be my time for socialising” (Patient). Another woman felt that one night off would give her “a bit more freedom, ‘cause I haven’t got enough hours in a day for everything” (Patient). As well as the time on the machine, people need to connect and disconnect themselves and set up a tray using aseptic techniques beforehand. This was the element that one patient found most challenging. “What fazes me is thinking…I've got to go set my tray up and,...wiping...sometimes I think, oh I wish somebody would come and do it for me” (Patient).

The time constraints and physical restrictions for some patients seemed to give rise to psychological sequelae. These patients despite being on PN for a number of years found it difficult to accept, which seemed to be fueled by how much control patients felt that they had over their lives. As one patient said “this rules my life and I hate it” ). Patients who had gone from being healthy to starting PN after an acute illness were the ones who most vehemently objected to the treatment. Although, they had been on PN for some time it had not become their new normal and they wanted their lives back. As one said “I hate it, absolutely hate it because I’m on three and a half litres, 12 hours, every single day, just don’t have a life.” (Patient). Patients who were chronically ill prior to PN were more accepting of the treatment, but this was not true for all. For example one patient who had Crohn’s disease for many years prior to PN said: “I try and get out of it… every time I go [to clinic], I say, can I have a night off?” (Patient). Patients who found PN difficult to accept were the most keen to explore taking teduglutide as an alternative form of treatment.

The other reason that patients gave for wanting to reduce PN was thinking about their long-term health. PN comes with different side effects and patients mentioned that they wanted to avoid these. A couple of patients said they wanted to avoid central venous catheter infections. One patient specifically mentioned liver disease which she already developed from being on PN “I went for a five-month scan in July and they came back with Stage 4 liver fibrosis. So, if I don’t get off this, it’s only going to get worse” (Patient). However, the aspiration to stop PN could be questioned for some participants given their level of clinical dependency on the treatment.

Nothing to lose trying teduglutide

Patients felt that they had nothing to lose by trying the drug; if teduglutide did not work then they could go back to how they were before so why not give it a try. As one patient said “If it doesn’t work, I’m not any worse off” ). If they did not take the option they thought they might regret it. “I've got to try it...I don't want to look back in years and say I wish I'd gone on that trial now” (Patient).

This attitude seems to come from patients managing their expectations and not focusing too much on the benefits if the drug was successful. Some patients did allow themselves to be hopeful, as one patient said “I’m determined it’s going to work” ) and another commented “I’m feeling positive about it” ). Most however managed their expectations to try to avoid disappointment, even those who had high hopes of success. As one patient said “I have high hopes, but at the same time, I can’t get hopeful” as “I might be ill with it and I might need to come off it” ). Some patients did this more than others, hardly allowing themselves to be hopeful at all “I’m trying to think that it’s not going to do anything for me. If it works it’s a consolation” (Patient).

Relatives were even more circumspect about what the medication might achieve as they did not want their relative to be disappointed. A family member said “realistically, listening to [Doctor], I don’t think it’s going to give her any nights off…the most I think it’s going to do, is reduce the fluids, maybe the hours on it” . Another family member said that they were keeping their expectations low.

Support from relatives

Relatives were reported to be important in the patients’ decision making process. Patients commented that they discussed taking the drug with people who were close to them. Mostly, relatives were supportive: “My daughter and my best friend x [think]…I should go for it. They're great my friends, they're so supportive” (Patient). This support encouraged patients in their decision to take the drug. However, one reported that his family were not that keen on him trying it “I don’t think my mother really wanted me to do it because she said, well, if you’re alright as you are, you manage, why do it” (Patient).

All three relatives interviewed wanted to support the patient in their decision, due to the potential benefits that may come from the drug. One family member thought that the drug could lead to growth of the patient’s intestines which could be beneficial if she needed an operation in the future. “If she goes onto the drug...and it grows her bowel, even a few inches, ’cause she’s got so little bowel, everybody’s reluctant to do any operations on her. And I’m thinking…that it might be enough that if she does have to go for an operation” . Another family member supported the patient’s decision as she was so keen to give the drug a try saying “she’s got to try it” .

One relative, although supportive, had reservations. On one hand, he was supportive of the patient’s decision saying “I think it will help him long-term” as he felt it would prevent him having to rely on nursing support if he could not self-manage PN in the future. However, he brought up the concern the patient mentioned about losing benefits; ”my issue was going to be if he was declared fit to work again, he’d be a lot worse off, and I know it’s bad saying but I mean I think he’s 57… So, who’s going to take a 57 year old on for work? Nobody is really” (family member).

Helping others in the future

Another reason for trying the medication was that it might help others in the future. Three patients mentioned this as an incentive for them to try teduglutide. Patients had the view that they had benefitted from past research and even if it turned out that this was not suitable for them, they were giving to prospective patients. “If it doesn’t work for me, the information and different things that you’ll get off me…it’s all maybe going to help somebody else in the future.” (Patient).

*Reasons against taking teduglutide*

The reasons that patients considered not taking the drug were that they accepted being on PN, the side effects that came with the drug and the extra monitoring that it entailed.

Accepting PN

Some patients were ambivalent about starting the medication. These were predominantly patients that had been unwell with Crohn’s disease prior to PN, who had found it easier to accept PN on commencement as it made them feel physically better. For some of these patients, PN was the ‘new normal’; it was difficult to think about life prior to PN, and they had completely adapted their life to accommodate it. The greater the acceptance of PN, the greater their ambivalence towards teduglutide “Well at first, I said, oh I'm not so sure at my age, and I don't want to rock the boat because I feel so well. And I thought about it and I umm’d and ahh’d” (Patient). One patient who did not feel that PN had any negative impact on his life was particularly ambivalent. “[PN] doesn’t impact it that much. That’s why I was really humming and harring” (Patient). However, in the end all the patients decided to take the drug.

Monitoring whilst taking teduglutide

Monitoring teduglutide is quite complex, requiring fluid balance charts twice weekly at home and more hospital visits than normal in order to stabilise patients safely. This monitoring could be viewed negatively. For the patient relying on his relative for lifts to appointments, the extra clinic visits were a major disadvantage. Another patient commented that all the extra monitoring required at home was “a bit full on” (Patient).

However, patients understood the need for the increased monitoring and accepted it. This included the patient who commented on the amount of monitoring being done; “I understand why it’s got to be done…to be honest and it gives you reassurance anyway they’re keeping an eye on you” (Patient). Even the extra clinic visits were not a disadvantage for all patients. One patient actually viewed them positively. She lived a long distance from the hospital so would stay overnight for clinic visits so treated it as short break combining the hospital visit with other things. “So it’s just like a wee overnight trip from home…We’ll go to the shops and different things like that, and then we’ll go home. So just to make it positive.” (Patient).

All of the relatives interviewed were involved in driving their family member to the hospital for appointments. They were quite happy to do this saying they did not mind the driving; “I’ll take her anywhere. I’ve always said that, so I’ll always do” (family member). Some of them took the opportunity to do other things. One relative would drop the patients at the hospital and go to a nearby shopping centre with his partner “We go and have something to eat. We have a look round and… It’s not as if we’re stuck in a hospital all day” . Another relative looked at it as a short break, “It’s away from the everyday norm” .

For both patients and relatives, ultimately the monitoring involved was not a reason to decide against taking the drug. In fact, it gave them reassurance that they were being properly cared for and mitigated concerns about side effects.

Side effects

Patients were aware that the drug could cause side effects but generally seemed unconcerned as they would be closely monitored. Due to this monitoring, it appeared that consideration of side effects was a minor issue for patients in the decision about taking the drug. This minimising of side effects came in different ways from patients, for example some thought that there were risks associated with everything and side effects might not happen to them. “They’ve told me there is risks, but life is a risk. So, as long as they monitor me…I’m not bothered” (Patient). Patients also felt that if they did incur side effects then there were ways of dealing with them “I get it, it could be like intense cramp, but [doctor said] if your pain relief isn’t working, we can work round that” (Patient). They also thought if the side effects became too much for them to cope with as they would just stop taking the drug “if there’s any problems…you’d stop straightaway” (Patient).

One side effect is a slight increased risk of gastrointestinal cancer. Two patients said that they were slightly fearful about this, “I mean, it was a worry when they said there’s…the cancer side of it” (Patient). They thought the risk was worth taking. “I know the side effects to this, I’ve read it and whatever. Colon cancer, stomach cancer. I’ve spoken to my mum about it, I’ve spoken to my partner about it, and it’s a chance I had to take” (Patient). These were patients who had spoken about difficulty they had in accepting PN so for them the benefit the drug might bring was worth the potential risk of cancer.

Relatives however had greater concerns about side effects. A family member said he was concerned but felt “there’s not enough research into it to know exactly what all the side-affects are going to be” . This was despite information about side effects being given to him and the patient verbally by the doctor and in writing. One family member hearing about side effects questioned the patient’s commitment; “when they said the side effects of whatever, it can be this, this and this, I said, are you sure you want to do it? She says, yes” .

*Views on succesful outcomes*

Whilst all patients wanted to reduce or stop PN, they varied on what they thought was a successful outcome from the drug. Some patients thought a positive benefit would be a reduction in fluid meaning that they would have fewer hours on PN, or a night off “One night would do me” (Patient). Others would be disappointed if they did not stop PN altogether. For example, one patient on PN twice weekly said that although not having to have PN would be helpful for family dynamics, her main motivation for wanting to stop was that the central venous catheter could be removed. “Having this line, I hate it. I hate it… Taking me off the TPN, yes, it will be wonderful, don’t get me wrong because I’ll get part of my life back again… until this line is out of me, I still can’t have a bath, I still can’t go swimming, I still can’t go on holiday so it ain’t going to make a lot of difference... In a way that makes me disabled. I feel disabled” (Patient).

**Discussion**

Teduglutide is a treatment that can reduce patients’ need for PN and as such is a helpful addition to treatment for SBS-IF. This is the first study looking at the patients’ decision making process for taking teduglutide and how family members inputted into the decision. This decision was informed by how much patients accepted PN; the more they accepted it the more ambivalent they appeared about trying the drug.

The patients in this study had been living with SBS-IF for at least two years and fell into two groups of being more or less accepting of PN with patients less accepting of PN keener to try the drug. Patients with chronic diseases discuss the idea of a “new normal”; the disease disrupts their normality as activities and routines are upset, but gradually new routines are put into place (27-30). Some patients in this study had managed to navigate the journey into a new normality better than others and these patients were more ambivalent about trying the drug. In the group of patients who found accepting PN most difficult, a number had become acutely unwell and unexpectedly found themselves with SBS-IF; notably, it has been discussed previously that patients who have a rapid onset of IF have a poorer quality of life (31). These patients were more enthusiastic about taking the drug.

Although, some patients were more enthusiastic about starting teduglutide, all of the patients took part in active decision making on whether or not to commence the drug. Having informed consent from patients is obviously important prior to any treatment. However, it has been noted that patients deciding to take part in clinical trials may be actively deciding or may be passive participants, deciding on the basis of others’ opinions without considering the risks and benefits themselves (32). Passive participation was clearly not the case in this instance; the patients bar one discussed the decision with relatives and all carefully weighed up the risks and benefits. This concurs with another study that found patients with IF will carefully consider alternative treatments to PN (33). The decision to take teduglutide was not a straight forward one for most either because their disease was well managed and they did not want to upset the balance or because of the side effects associated with the drug. This can be contrasted with decision making for PN. Patients discussing their experience of PN, refer to the treatment as life saving (9, 34, 35). However, they do not discuss deliberating about the decision to start PN, probably because it was driven by clinical need.

Having decided to take the drug, all patients engaged in managing their expectations of the treatment (36). Patients discussed reducing the number of nights of PN or stopping PN altogether, but tempered this desire with lower expectations of what they actually thought would happen. They seemed to be doing this to protect against disappointment. Similarly, Stone et al found in interviewing patients from four randomised control trials (37) that patients distinguish between their actual expectations and what they wished could happen. The difference between expectations and desires is something that Uhlmann et al. has drawn; an expectation is something that patients think is likely to happen whereas a desire is a wish, being what they would want, but not necessarily think is going to occur (36).

Another reason that patients gave for taking part was helping others. Patients altruistically wanting to give back to other patients and science in general is a well-documented reason for taking part in studies and trying new drugs (38). It is also documented that participants take part for a mixture of reasons of helping others and helping themselves. Helping themselves for patients in this study seemed to have two elements. The first and most prominent was that they would reduce their time on PN. However, there seemed to be a second psychological element: the knowledge that they may be helping others in future may provide an insurance policy against any disappointment if the treatment did not work for them. In this case the patients were gaining the positive feeling of helping others which could act as compensation for potential lack of success for them.

What patients considered a successful outcome varied from patient to patient. This highlights the need for patient-centred care, involving clinicians taking time to understand what is important to a particular patient and their goals (39). As tedglutide has moved from being used in clinical trials to the real life setting patient-centred care and shared decision making to start the treatment are vital (40, 41), not least because patients may have unachievable expectations which need discussing before they embark on a therapy. In addition, patients did not find it a straight forward decision and need to balance their preferences against the risks of the treatment.

*Strengths and Limitations*

A strength of this study is that relatives as well as patients were included in the interviews, particularly as patients commented that relatives were important in their decision making process.

A limitation is that all the patients in this study had made the decision to take teduglutide so their views may be different from patients who choose not to take the drug. Therefore it would be interesting to investigate the views of those patients. Also the patients were treated at one hospital and the numbers are small. However, although the numbers are small, similar themes were emerging from the patients, and notably the split in views between the patients started on PN due to acute or chronic illness echoes what is known in the literature (31). Therefore, it is likely that patients having PN would have similar issues. However, it would be beneficial to research this further.

*Conclusions*

Patients were motivated to reduce PN and take teduglutide. They considered that potential benefits outweighed any disadvantages and side effects. Relatives were by and large supportive of their decisions, although they had a few more reservations. However, some patients had unrealistic expectations and clinicians need to provide patient-centred care to explore what patients would consider a successful outcome to ensure that it is achievable.

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**Figure 1. Patients reasons for and against teduglutide**

PN – parenteral nutrition