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Patients' experiences with methylcobalamin injections in amyotrophic lateral sclerosis

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Abstract:

BACKGROUND AND OBJECTIVES: Amyotrophic lateral sclerosis (ALS) is a progressive motor neuron disease with no definitive treatment. Vitamin B12 is not a Food and Drug Administration-approved treatment in the United States, although it has been prescribed off-label as ultra-high-dose methylcobalamin, which has been shown to be safe and effective in slowing functional decline in patients with ALS. This study evaluates the impact of Vitamin B12 injections on the quality of life of five patients.

METHODS: Semi-structured interviews were conducted with the patients and caregivers. The data was carefully read, coded, and organized into themes and sub-themes by two independent researchers.

RESULTS: The study found four themes and 11 subthemes from the data, including initial circumstances, administration of the injection, subjective experience with Vitamin B12, and outcomes and expectations. All participants recognized some benefits from Vitamin B12 injections, specifically increased energy, reduced fatigue, and improved balance. However, some patients had difficulty monitoring its specific effect due to the progressive nature of the disease.

DISCUSSION: The flexibility offered by this intervention is beneficial for patients with declining mobility and strength who wish to adapt their treatment to their schedule. This work is a modest call to fill the existing gap in the literature and push for more randomized controlled trials investigating and clarifying the effects of Vitamin B12 injections on disease progression, muscle function, and quality of life in a small but diverse pool of patients with ALS.

Keywords:
ALS, B12 injection, patient experience

Introduction

Amyotrophic lateral sclerosis (ALS) is a motor neuron disease characterized by the degeneration of both upper and lower motor neurons. Recent population-based studies have found a global prevalence of ALS between 4.1 and 8.4/100,000 persons.[1-5] In the United States, a prevalence of 5.2/100,000 has been reported in 2015 based on the US National ALS registry.[6] It is a sporadic disease in most affected patients, but about 10% of cases are familial.[7] Clinical presentation varies, and common symptoms include muscle twitches, cramping, and gradually increasing weakness.[8] The disease is fatal, and the burden of illness on patients, family members, and caregivers is substantial, with increasing costs associated with escalating disability and the eventual need for assisted medical care. There is no definitive treatment for ALS, but certain drugs are prescribed for patients living with the disease. Riluzole was the first Food and Drug Administration (FDA)-approved treatment in 1995,[9] and was shown to impact mortality, extending median

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survival by 2 to 3 months.[10] Edaravone was approved in 2017 in the United States after showing efficacy in a small subset of people who experienced a significant decline in ALSFRS-R score compared with placebo.[11] It can be given either as an oral suspension or as a 60-mg intravenous infusion over an hour. Treatment is initiated with daily dosing for 14 days, followed by 14 days of treatment with subsequent cycles of daily dosing for 10 days within a 14-day period, followed by 14 days of no treatment.[12] In September 2022, a new drug developed by Amylyx Pharmaceuticals was approved by the US FDA for the treatment of ALS.[13] AMX0035 is a fixed-dose oral co-formulation of sodium phenylbutyrate and tauroursodeoxycholic acid that was found to slow the decline in ALSFRS-R total score in the multicenter, double-blinded, randomized CENTAUR trial.[14]

Several experimental therapies targeting various aspects of the posited pathophysiology of ALS are being explored for use in patients. One such therapy is methylcobalamin, which was found to increase the compound muscle action potential amplitudes in patients with ALS and delay the progression of motor symptoms and neuropathological changes in a mouse model.[15] More recently, a randomized clinical trial in Japan showed that ultrahigh-dose methylcobalamin was safe and efficacious in slowing functional decline in patients with ALS.[16]

Methylcobalamin is an active form of Vitamin B12, a water-soluble compound that plays a key role in the normal functioning of the nervous system.[17] A deficiency of Vitamin B12 is associated with conditions affecting the central nervous system, such as subacute combined degeneration of the spinal cord.[18] In cell culture studies, it has been shown to ameliorate oxidative stress, glutamate toxicity, and apoptosis, all of which are believed to play essential roles in ALS progression.[19] Riluzole is believed to act in part through the reduction of glutamate-induced toxicity.[20] Vitamin B12 is not an FDA-approved treatment in the United States. Its off-label use necessitates that patients incur out-of-pocket expenses to obtain it. It is typically manufactured by specific pharmacies and shipped as a sealed frozen package with several vials containing a 25-mg injectable dose.[21] Patients are advised to inject daily. In our study, patients injected with 50 mg of B12.

While current research has been focused on identifying the pathophysiologic mechanisms and clinical effects of these interventions, little research has examined patients' perspectives on experimental therapies. Patients provide valuable insight into the overall adequacy and safety of their care based on their individual experiences. This is of particular significance in patients with ALS who have specific requirements and can provide important details on their care that cannot be captured by staff, despite they have tremendous potential to inform policy and practice.

The primary objective of our study is to understand the impact of Vitamin B12 injections on the overall quality of life of patients receiving them. In particular, one aim is to assess patients' difficulty with self-injection and the impact on their daily lives. Their insights can be used to provide other patients with first-hand accounts of what it is like to receive such treatments. A second goal is also to examine the experiences of caregivers who assist patients with Vitamin B12 injections and perceived barriers to receiving treatment.

Methods

Participants

This study was approved by the Yale University Institutional Review Board. A search of the Yale ALS Clinic identified 50 patients with ALS who have received Vitamin B12 injections as part of their treatment regimen for at least 2 months. Patients who met these criteria were contacted and recruited on a contingent basis via an opt-in approach. An initial E-mail describing the study was sent, requesting that interested patients respond to the team to be interviewed. Two follow-up E-mails were then sent. Five patients responded and were recruited for the next phase of the study [Table 1].

Clinical trial registry

No clinical trials were involved.

Data collection

A researcher trained in qualitative methods (KS) conducted semi-structured interviews to explore patients' and caregivers' perceptions and experiences with B12 injections. The interviews lasted between 31 and 50 min (average 34 min), were audio-recorded, and transcribed verbatim. Participants chose the date, time, and whether to meet over Zoom or the telephone. They were assigned a unique identifier to preserve their anonymity, and no identifying information was linked to them. An interview outline was created and approved by all authors to ensure coverage of the topics of interest.

Data analysis

Two independent researchers (LS and KS) used

Table 1: Patient demographics

Patient	Age	Gender	Riluzole	B12 injection
1	68	Male	Yes	Yes
2	41	Male	Yes	Yes
3	40	Female	Yes	Yes
4	58	Male	Yes	Yes
5	66	Male	Yes	Yes

qualitative analysis with an inductive approach to analyze the data. The interview transcripts were carefully and repeatedly read to ensure in-depth familiarization with the content. Files were uploaded to NVivo (Manufacturer: Lumivero, Denver, Colorado, USA) V.12 software to facilitate the data analysis process. This was followed by the generation of initial descriptive codes, which were then mapped onto the data and frequently revised along with their respective definitions. Codes were then assembled into preliminary themes that captured features and patterns of the data. These themes were subsequently discussed and reviewed by the authors, thereby generating themes and subthemes of the analysis. In the next step, the themes were further refined and given proper titles. Finally, examples were selected to illustrate the thematic framework.

Results

Four themes and 11 subthemes were developed from the data [Table 2]. They are discussed below, with supporting statements from participants' interviews.

Initial circumstances

All patients began the interview by talking about the first symptoms they experienced and their paths to being diagnosed with ALS. Symptoms included a noticeable change from baseline, particularly in two patients who engaged in regular physical activity (e.g., race runner, golf player). Additional presenting symptoms comprised balance problems, recurrent falls, and muscle spasms. Two patients mentioned they were referred to the Yale ALS Clinic and two others sought a second opinion after the initial diagnosis because of the seriousness of the disease and the long-term implications of the diagnosis.

Table 2: Frequency of identified themes and subthemes during interviews

Themes and subthemes	Total
Initial circumstances	79
Diagnosis	15
Decision to start	33
Source of information	31
Subjective experience with Vitamin B12	117
Desirable effects	61
Undesirable effects	29
Dosage	27
Administration of the injection	62
Caregiver involvement	34
Logistics of getting the injections	22
Logistics of disposing of the needles	6
Challenges	37
Financial barriers	23
Suggestions	14

"I started noticing some symptoms back in the fall of 2017. I was a lifelong runner and there was something going on with my mechanics that gave me pause. Then I ran a race and did really, really bad, so I knew something was up."

All patients reported first hearing about Vitamin B12 injections from their neurologist at Yale at the time of diagnosis. Two patients carried out additional independent research to understand more about this treatment, with the support of their spouse and family members. One of them was particularly knowledgeable about the recent literature and evidence-based practices. Another patient shared his unwillingness to look up information on Google because of the toll it was taking on his mental health and the availability of reliable information from his providers.

"B12 came up and I said, well, I'm in. Whatever it takes and every little bit is going to help, so we got right on the B12."

Participants stated that the decision to initiate this treatment was based on the absence of significant side effects and the potential positive outcome on quality of life. The decision was also helped by the participants' perception of their condition, in that any treatment could only potentially provide a positive or neutral outcome when compared to the negative prognosis of this terminal illness. Specifically, three patients mentioned that it would not harm them to start it, with one of them pointing out that Vitamins are a natural substance.

"I figured it wouldn't hurt and I could use the boost."

Administration of the injection

Four caregivers were spouses and one was the patient's mother. All five played a role in the injection process, ranging from taking it out of the refrigerator and preparing the needles to performing the entire procedure. Two were experienced nurses who helped with independent research regarding treatment options. None of the caregivers reported any difficulties or burdens related to the Vitamin B12 injections.

"I think it's just routine, it's no big deal. It's like getting him out of bed in the morning. It's not an issue at all."

All patients stated that the process of obtaining the injections was straightforward. Disruptions are minimal and do not interfere with their individual injection schedules. All have their injections delivered to their place of residence. One patient commented on maintaining a 7-day supply in case there are shipping delays.

"Instead of shipping it in two to 3 days, the pharmacy will ship it in a week or more, and I'll be out. So, I have a 7-day reserve just in case."

Two participants commented on the disposal process. Although some patients are aware that used needles constitute biohazardous waste, the disposal procedure is not entirely clear.

"You're not supposed to just throw them in the trash, so we have a stockpile. We have a new biohazard container, but it's full. I think our local police station will take them."

Subjective experience with Vitamin B12

All participants recognized some benefits from Vitamin B12 injections. The most frequently reported favorable effects were increased energy, reduced fatigue, and improved balance. One patient pointed out the difficulty in monitoring the impact of his medications due to the progressive nature of the disease. All patients except this one noted that on days they do not receive B12, they feel less energized and notice the difference.

"Poor balance is my most significant symptom. After a B12 injection, I feel more sure on my feet."

Mild pain at the site of injection was reported as a minor discomfort by three patients. Only one patient reported having to decrease the frequency of Vitamin B12 injections due to it causing her to develop "thick, hard acne" postinjection. She also noted muscle stiffness with increased frequency despite the boost in energy. Another patient observed that his hair and nails grow faster when using Vitamin B12, although he did not find it bothersome.

"I have more energy on the days I take the injections but I also feel a little stiffer. So, it's just about balancing the energy versus the feeling stiff. If we don't have anything to do on a given day and it's better to just relax, then maybe we wouldn't do the injection."

In all interviews, patients indicated that they adjusted the frequency of injections based on their personal experience with the treatment. For example, one patient reduced the frequency of injections in response to the perceived skin manifestations described above. Another patient stepped up the frequency of injections because of their positive effect on his overall energy, and daily injections were recommended by other people with ALS.

"Initially, I did the injections twice a week. It was easy to tell the difference in my energy once I started doing them every day."

Challenges

All patients acknowledged that the insurance coverage of the product was insufficient and the cost was very high, regardless of self-reported financial status. Three patients disclosed that the financial burden impacted their decision regarding the injection schedule.

"The cost poses a barrier to how often I take the shots now. A daily dose would cost almost $ 300 a month."

"Insurance does not cover it, although that would be nice."

Participants suggested the standardization of needle sizes, mechanisms, and the hardware required to perform the injection to facilitate the process. Two patients called for FDA approval to ensure adequate provision, widespread supply in local pharmacies, and encourage insurance coverage of the product. One patient stated that the paucity of literature on this treatment creates discrepancies in prescribing it and physicians' attitudes toward it.

"It would be good to have a standard syringe, because otherwise, you have to learn every time."

"When I told Dr. X I was taking Vitamin B12 injections, he kind of rolled his eyes."

Discussion

This study explores the experiences of people living with ALS and their caregivers with Vitamin B12 injections and the barriers to accessing this product. Four general themes emerged from our data: Circumstances leading up to the initiation of treatment, administration of the injections, clinical effects of Vitamin B12 with respect to their condition, and the challenges faced with this treatment.

First, all patients initially heard about Vitamin B12 injections from their neurologist. Their decision to start was informed by the clinical encounter and the insights shared by the physician. Most patients elected to proceed because of the low-risk profile of side effects and the incremental benefit to their quality of life in the face of an invariably fatal disease.

Second, caregivers appear to play a role in the injection process, with varying degrees of involvement. The extent of participation seems to be related to the stage of the disease and motor function.

Third, the data demonstrate a generally positive attitude toward Vitamin B12 injections among participants. They all have a satisfactory experience with the injections and expressed an interest in indefinitely continuing. Furthermore, the frequency and timing of the injections were managed at the patients' discretion since the regimen lacks uniform guidelines. The autonomy resulting from this flexible scheduling in the context of a debilitating disease is highly convenient for patients and

enables them to complete injections whenever suitable with their planned activities for the day.

Finally, the significant challenges identified with Vitamin B12 injections in the setting of ALS were the lack of insurance coverage and the inconsistency in the type of syringes delivered, particularly in the setting of COVID-19 supply chain disruptions.

Due to the infrequent and off-label use of Vitamin B12 injections in patients with ALS, not all providers present it as a viable therapeutic option. Expanding the literature surrounding the benefits and positive patient experience with Vitamin B12 therapy can potentially promote its endorsement by providers during clinical encounters. Therefore, it is essential to advocate for the availability of this adjunctive therapy among providers to improve patients' quality of life.

Most of the everyday challenges faced by people living with ALS relate to their quality of life, from symptoms and disease progression to coping with the ongoing diagnosis of ALS and gradual loss of independence. As a result of the flexible nature of Vitamin B12 injections, patients are empowered by being given decision-making authority over the treatment regimen, resulting in a greater sense of autonomy and favorable engagement with the injections. They can be flexible for usage in times when injections would be difficult to incorporate into their routine. In addition, they develop personalized strategies to address their symptoms and optimize the timing of treatment effects, as they can independently decide on the dates and times of injections. The most commonly reported positive effects of the injection are a boost in energy and improved balance control, which is a major concern in ALS.[22] Participants noted no significant side effects. Overall, this study demonstrates that this noninvasive adjuvant therapy modality is well tolerated by participants and valued.

Off-label prescribing involves the use of certain medications for conditions other than the ones for which they were initially intended. Although they are generally safe and effective, they are not supported by the same body of evidence and research as FDA-approved products.[23] Providers must consider the potential benefits and risks of off-label drug prescriptions when making decisions about patient care and must inform their patients of any potential risks. The upside of off-label drug use is the opportunity for physicians to be proactive in providing the most appropriate, up-to-date, and individualized care for their patients. This practice can also generate significant value for patients by providing greater access to treatments that the FDA has yet to approve for their condition. These treatments may also be helpful for patients who have not responded to other therapies or provide alternatives for patients who do not have other treatment options available.[24] The participants in this study appeared to fall within the latter group. Several mentioned that they valued having additional opportunities beyond the standard of care and intended to continue using the B12 injections indefinitely.

Insurance coverage for the off-label use of medications is an important consideration. In general, these drugs are not covered by insurance, and patients are responsible for the total cost.[25] At this time, the financial burden of Vitamin B12 shots is borne exclusively by patients and constitutes an additional challenge in managing their condition. Its use is not covered by most insurances, is not approved by the FDA, and it is not widely available in pharmacies. In fact, all patients reported having it shipped to their house from an out-of-state pharmacy. Although the delivery service was reliable, two patients stated that they had to stock up and purchase their injections in bulk quantities in advance to accommodate any delays.

Further research is needed to substantiate the findings of the Japanese study on a larger scale and with a more diverse patient population. However, for a disease for which additional treatments are urgently needed, the small effect of methylcobalamin on slowing the decline of ALSFRS-R in early ALS is encouraging.[26] In addition, any patients with ALS are already consuming Vitamin supplements in conjunction with prescribed treatments,[27] and it is essential to consider this aspect of their disease management. The value of patient-reported outcomes (PROs) and follow-up to optimize disease management is well established.[28] Monitoring PROs and patients' subjective experiences with ALS is an integral aspect of comprehensive care. The practice provides unique insights into their experiences and the disease's impact on their daily lives. By tracking PROs, clinicians also gain a better understanding of overall quality of life, functional ability, and psychological health. This information can be leveraged to develop personalized interventions and regimens tailored to each patient's unique needs. Ultimately, monitoring PROs and the subjective experience of patients with ALS can lead to improved outcomes and quality of life for those living with the disease. This study is a modest call to seek financial coverage by payers and regulatory endorsement to expand access to Vitamin B12 injections while better monitoring supplement use in ALS.

One of the limitations of this study is the small sample size. However, this is a particularly challenging problem when it comes to conducting interviews with patients with ALS as they often have speech impediments. In addition, our inclusion criteria were quite restrictive, further limiting the number of eligible participants. As

a result, the small sample size may not be representative of the larger population of patients with ALS. Despite this limitation, we have taken the necessary steps to ensure that all interested participants may take part in this study if interested. This study will serve as a pilot study for future larger studies.

Conclusion

This pilot study examines the experiences of people living with ALS and their caregivers with Vitamin B12 injections and the barriers to accessing this product. Four main themes emerged from the data: The circumstances leading up to the initiation of treatment, the administration of the injections, the clinical effects of Vitamin B12, and the challenges faced with this treatment. The study found that patients heard about Vitamin B12 injections from their neurologist and decided to start the treatment because of the low risk of side effects and the potential benefit to their quality of life. Caregivers play a role in the injection process, but the degree of involvement varies depending on the stage of the disease and motor function. All participants recognized some benefits from the injections, with the most frequently reported favorable effects being increased energy, reduced fatigue, and improved balance. However, the lack of insurance coverage and inconsistent syringes were significant challenges faced by participants. The study suggests that expanding the literature surrounding the benefits and positive patient experiences with Vitamin B12 therapy could promote its endorsement by providers during clinical encounters and improve patients' quality of life.

Author contributions

All authors contributed to writing/revision of the manuscript, data collection, and approval of final submission. Initial concept idea for study was derived by Drs. Zubair and Khokhar.

Ethical approval

This study was IRB approved by the institutional review board at Yale (2000029865, dated on 2/17/2021). The study was done in compliance with this approval and research standards, and was performed in accordance with the Declaration of Helsinki.

Declaration of patient consent

Written patient consent was not required by the IRB. Patients provided verbal consent for the study.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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