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NEUROPATHIC PAIN SECTION

Original Research Article

The Role of Qutenza® (Topical Capsaicin 8%) in Treating Neuropathic Pain from Critical Ischemia in Patients with End-Stage Renal Disease: An Observational Cohort Study

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Disclosure: Ethical approval for this trial was granted by the West of Scotland Research Ethics Committee and the Medicines and Healthcare Products Regulatory Agency (MHRA). Research has been carried out in accordance with the Declaration of Helsinki.

Trial registration: The trial was prospectively registered with clinical trials databases (EudraCT: 2012-001586-32; and NCT01704313).

Abstract

Objective. Current treatment strategies for painful critical ischemia in patients with end-stage renal disease (ESRD) are suboptimal. A drug that is non-renally excreted has minimal systemic absorption and does not require dose adjustment in renal failure is attractive. The aim of this study was to evaluate the safety and efficacy of Qutenza® (topical capsaicin 8%) for chronic neuropathic pain from critical ischemia in patients with ESRD.

Design and Setting. A prospective cohort study was conducted in a single-center, university teaching hospital.

Patients. Twenty patients with ESRD were treated with Qutenza® for neuropathic pain from critical limb ischemia.

Methods. Patients were followed-up at 1, 6 and 12 weeks post-treatment. The primary end point was the difference in visual analog scale (VAS) between baseline and week 12. Secondary end points were Brief Pain Inventory questionnaire (BPI) scores, quality of life assessment (EQ-5D) and patient global impression of change (PGIC). Safety and tolerability data were also collected. The trial was prospectively registered with clinical trials databases (EudraCT: 2012-001586-32; NCT01704313).

Results. There was significant reduction in VAS from baseline to week 12 (-20+/-7%; $P = 0.02$). There was a significant reduction in all seven domains of the BPI. Quality of life also improved at 12 weeks following treatment in two of the EQ-5D domains (mobility and pain). Qutenza® was well tolerated with no significant side effects in this patient cohort, which included 20% diabetics.

Conclusions. In this small, observational study Qutenza® treatment has been shown to be effective and well-tolerated to treat neuropathic pain from critical ischemia in patients with ESRD.

Key Words. Neuropathic Pain; Renal Failure; Capsaicin

Introduction

Peripheral vascular disease (PVD) is very common in patients with end-stage renal disease (ESRD). A clustering of risk factors for ESRD and PVD, along with the direct deleterious effects of renal failure and dialysis on the arterial tree, result in nearly three-quarters of patients on hemodialysis having radiographic and/or symptomatic evidence of PVD [1].

Peripheral arterial disease and critical ischemia are notoriously difficult to treat in patients with renal failure. The distribution of arterial disease in patients with ESRD tends to be distal with limited options for revascularization; advanced disease and extensive co-morbidities limit surgical revascularization in those patients who do have proximal disease [2] and calciphylaxis (a process of calcification within the small vessels unique to patients with end-stage renal failure) has few effective treatments [3]. Often the only treatment options are symptomatic with strong analgesics or amputation performed for the relief of pain.

Effective pain relief can be difficult to achieve in patients with ESRD. The active metabolites of most opiates are renally excreted and side effects, such as confusion and drowsiness, are common in patients with renal disease. Furthermore, the adjuvant agents (e.g., gabapentin and pregabalin) recommended as first line treatment for neuropathic pain by most guidelines [4] have not been investigated in clinical trials in patients with ESRD [5].

Qutenza® (topical capsaicin 8%) is an advanced dermal application system designed for rapid delivery of capsaicin into the skin. The high concentration of capsaicin results in reversible desensitization of TRPV-1 expressing cutaneous sensory nerve endings and reduction in nerve fiber density in the epidermis [6]. The resulting pain relief is long-lasting (12 weeks after a single application) [7,8]. Phase III studies have demonstrated a significant reduction in neuropathic pain in patients with post-herpetic neuralgia [9] and HIV neuropathy [6,10] with a good tolerability profile. The Qutenza® safety and efficacy in peripheral neuropathic pain (QUEPP) study showed a 36.6% reduction in pain scores at 12 weeks in patients who had had pain for less than 2 years [11,12]. More recently, a large, randomized phase IV study demonstrated non-inferiority of Qutenza® compared to pregabalin in patients with undefined painful peripheral neuropathies [13].

Critical limb ischemia gives rise to a clinical picture that closely mimics neuropathic pain and is multi-modal, caused by a variety of conditions including tissue ischemia, nerve compression and direct nerve ischemia [14]. It is notoriously difficult to treat, particularly in patients with established renal failure in whom other analgesic agents are poorly tolerated. A drug, such as Qutenza® that is not renally excreted, has minimal systemic absorption, and does not require dose adjustment in renal failure is an attractive treatment option for patients with renal failure.

The aim of this study was therefore to evaluate the safety and efficacy of Qutenza® (topical capsaicin 8%) in relieving chronic neuropathic pain from critical ischemia in patients with ESRD.

Methods

Study Design

A prospective, observational cohort study was designed to evaluate the role of Qutenza® (topical capsaicin 8%) in treating neuropathic pain from critical ischemia in patients with end-stage renal disease (ESRD).

Participants

Patients were recruited from the in-patient renal wards at Western Infirmary, Glasgow and out-patient hemodialysis units in the West of Scotland between April 30, 2013 and March 6, 2014.

All adult patients (over the age of 18 years) with ESRD (defined as an eGFR $<$ 15 mL/min/1.73 m^2, established on dialysis or with a functioning renal transplant) and critical ischemia (defined as rest pain affecting a major limb or digits on most days for $>$ 3 months) were eligible to participate. Patients were excluded of they had an allergy or hypersensitivity to Qutenza®, EMLA cream or any of the excipients; broken skin or active ulceration at the site of application; severe uncontrolled hypertension (systolic BP $>$ 200 mmHg); a proven cardiac event during the preceding 3 months; women who were pregnant or breast feeding; diabetic neuropathy resulting in a loss of sensation; a LANSS (Leeds Assessment of Neuropathic Symptoms and Signs) pain score $<$ 12; or had a lack of capacity or inability to provide informed consent or declined participation in the study.

Recruitment

Potential participants were identified by the clinical team. They were approached by a member of the research team and screened for eligibility. If eligible and willing to participate, written consent was obtained and treatment was administered in line with the manufacturer's guidelines [15].

Qutenza® Treatment

All patients were treated with a single transdermal application of Qutenza® (topical capsaicin 8%) (Astellas Pharma Europe B.V., Elisabethhof 19, 2353 EW Liederorp, Netherlands; MA Number: EU/1/09/524/001-002). Each 280 cm^2 patch contains 179 mg of capsaicin. Patients could be treated with a maximum of four patches (716 g of capsaicin). The exact dose administered was determined by the size of the area to be

treated. All patients received the treatment investigational medicinal product (IMP) only.

Blood pressure (BP) was recorded pre- and post-treatment and every 30 minutes throughout the procedure. Treatment was halted if the pre-treatment systolic BP was > 200 mmHg. The area to be treated (area of painful sensation) was marked out in conjunction by the patient and researchers and a mark drawn on the skin with an indelible marker. Any hair was removed from the area by cutting prior to treatment. A template of the area to be treated was traced using transparent paper. The area (and a further 2–3 cm beyond, to avoid overlap) was then pre-treated with topical lignocaine (EMLA) cream for 30 minutes. The EMLA cream was then removed and the area washed with soap and water. The area was dried carefully to ensure good contact between the Qutenza® patch and the skin. The template was then used to cut the Qutenza® patch to size and the Qutenza® patch applied for 60 minutes (30 minutes if the feet were treated). At the end of the treatment the Qutenza® patch was removed and the area thoroughly cleansed with soap and water and with the cleansing gel commercially packaged along with the patch. Patients were permitted to take any "rescue medication" as required during the treatment.

Data Collection and Follow-up

Patients were followed-up for a total of 12 weeks following treatment, with study visits on the first day following treatment and 1, 6 and 12 weeks post-treatment.

Basic patient demographics including age, sex, co-morbidities, cause and site of neuropathic pain, previous treatments, and pre-existing analgesic medications were recorded for all patients. Details of the treatment (size of area treated, duration of treatment, tolerance of treatment, immediate complications) were also recorded. An assessment of the skin reaction was made on the day following treatment and classified into categories (no erythema, mild erythema, severe erythema, mild blistering, severe blistering) by a single assessor who evaluated all patients.

The visual analog scale (VAS) [16,17] was used by patients to rate their pain on a numeric scale from 0 (no pain) to 10 (the worst pain ever). These were recorded at day 0, week 1, week 6 and week 12. The Brief Pain Inventory Questionnaire (BPI) [18] and EQ-5D quality of life score [19,20] were performed on day 0, week 6 and week 12. A Patient Global Impression of Change (PGIC) score was also recorded at week 12. The BPI is scored from 0 (no symptoms) to 10 (worst ever) and comprises of questions assessing the nature of pain and response to analgesic agents, and evaluates the implications of the patient's pain in seven domains (activity, mood, walking, work, relationships, sleep and enjoyment of life) [18]. The EQ-5D score evaluates the patient's assessment of their quality of life in five domains (mobility, self-care, ability to undertake usual activities, anxiety/depression, pain). It is scored from 1 (no symptoms) to 5 (severe incapacitation from symptoms) [20]. The PGIC score rates the patient's assessment of change in symptoms on a scale from 1 (no change) to 7 (a great deal better, and a considerable improvement that has made all the difference). All three are self-reported scales. A second investigator (different from the one applying the Qutenza® treatment) performed follow-up visits at week 1, 6 and 12 in an attempt to minimize any bias in self-reporting. Data were also collected on adverse events and concomitant analgesic medications at each study visit.

Data were collected on case report forms by the study team and then maintained in an electronic database by an independent Clinical Trials Manager based in the Department of Statistics, University of Reading (Berkshire, UK). Data were entered into the database at the University of Reading before being checked by an independent observer. A further third crosscheck was then performed by the research team to ensure accuracy of coding and data entry.

Data on adverse events were also reported to the local Pharmacovigilance Office at the Robertson Centre for Biostatistics, University of Glasgow in line with requirements of the MHRA.

Outcomes

The primary end point was the percentage difference in chronic neuropathic pain assessed by the visual analog scale between baseline and week 12.

Secondary end points were VAS at 1 week and 6 weeks, pain assessed by the BPI at 6 weeks and 12 weeks post-treatment, quality of life (EQ-5D) at 6 and 12 weeks, and PGIC at 12 weeks. Tolerability and safety of the Qutenza® treatment were also evaluated, by the need for "rescue medication" and BP changes at the time of treatment, skin changes in the early-post treatment phase and adverse events (mortality and morbidity, additional interventional procedures and hospital admissions).

Sample Size Calculation

A priori power calculation determined that a total of 20 patients would be required to detect a 30% reduction in VAS at 12 weeks from baseline based on a standard deviation (SD) of 30%, similar to that observed in previous studies of Qutenza® [7,8] with 80% power and significance 0.05, assuming 10% of patients would be lost to follow-up.

Statistical Analysis

Results were analysed using IBM SPSS Statistics for Macintosh Version 22.0 (Armonk, NY) Data were tested for normality using visual scatterplot and box plot analysis and Shapiro-Wilk test. Normally distributed

continuous data are described as mean (SD) and non-normally distributed data reported as median and inter-quartile range (IQR). Categorical data are reported as a percentage of the total number of patients. A Mann-Whitney U-test was used to compare continuous data and a chi-squared test to compare categorical data. It was assumed that without treatment, there would be no change in baseline pain score at 12 weeks and this null hypothesis was tested to determine if the change in pain score observed at 12 weeks was statistically different from zero. In order to ascertain the effects of treatment over time, a repeated measurements analysis was performed on data from week 1, 6 and 12. Analysis was performed on an intention-to-treat basis. Any missing data were confirmed to be missing at random and this patient was then excluded from analysis of the variable in question. A last forward approach was used towards drop-outs, as outlined in the a priori statistical plan. P values < 0.05 were considered significant.

Results

Recruitment and Follow-up

Twenty-eight patients were considered for participation in the study. Twenty-two met the inclusion criteria and were willing to participate. Two were excluded (one protocol violation; one withdrew consent prior to treatment). Twenty patients were therefore included for analysis. Two patients died during the 12-week follow-up period, leaving 18 patients who completed follow-up (Figure 1).

Patient Demographics

Mean patient age was 60+/−13.9 years (55% male). The majority of patients (75%; N = 15) had critical ischemia from irremediable small vessel disease, however it was a heterogenous patient group. Several patients had other coincidental potential causes of neuropathic pain (one carpal tunnel syndrome, one Sudeck's atrophy). Twenty percent (N = 4) were diabetic and 25% (N = 5) had a previous myocardial infarction. Most patients described their pain as aching (N = 14) and throbbing (N = 15). Fewer patients used terms commonly associated with neuropathic pain: burning (N = 8), shooting (N = 9), numb (N = 3). Table 1 outlines basic patient demographics. Eight feet, 10 upper limbs and two fingers were treated.

Tolerability of Qutenza® Treatment

Half of patients (N = 10) had some ulceration, necrosis or tissue loss. Areas of broken or ulcerated skin were not treated and the Qutenza® patch applied around these areas; however, if necessary the patch was applied areas of non-viable dry gangrene if this made the treatment technically easier to apply. Figure 2 outlines some of the limbs that were treated.

The mean size of area treated 220+/−60cm^2. Seventeen patients were treated with one patch, two patients required two Qutenza® patches.

All patients tolerated the Qutenza® treatment well and no one required to terminate treatment early. Two patients described a mild burning sensation and one described itching during the application. Only two patients required "rescue medication" (1 g paracetamol). There was no significant change in BP during treatment (mean change in systolic BP: +2.0+/−0.41 mmHg; mean change in diastolic BP: +4.0+/−5.1 mmHg; $P = 0.76$). One patient developed significant erythema immediately post treatment and six had mild erythema on removal of the patch. On day one post-treatment, 13 patients had no skin reaction, five had mild erythema, one severe erythema, and one mild skin blistering which self-resolved within 3 days.

Visual Analog Scale

Median VAS at baseline was 8 (IQR 6,9). Median VAS was 5 (IQR 4,6) at week 1, 5 (IQR 4,7) at week 6, and 6 (IQR 3,7) at week 12 (Figure 3). There was a significant reduction in VAS from baseline at week 12 (−20+/−7%; $P = 0.02$). There was a bimodal distribution of ΔVAS, with patients either having complete or near complete response to treatment or none (Figure 4). Fifty percent (N = 10) had a reduction in pain score of > 30% at 12 weeks. Forty-five percent (N = 9) had a reduction in VAS of > 60% at 12 weeks.

Brief Pain Inventory

Median BPI scores at baseline were as follows: general activity = 8 (IQR 4,9); mood = 7 (IQR 5.8); walking ability = 4 (IQR 4,7); work = 3 (IQR3,4); relationships = 6 (IQR 3,8); sleep = 8 (IQR 4,9); enjoyment of life = 9 (IQR 8,9). Median BPI scores at 12 weeks were as follows: general activity = 5 (IQR 3,6); mood = 4 (IQR 4,6); walking ability = 1 (IQR 1,6); work = 1 (IQR1,3); relationships = 4 (IQR 3,6); sleep = 4 (IQR 2,5); enjoyment of life = 5 (IQR 3,7). There was a significant reduction in each of the seven domains of the BPI at week 12 compared to baseline (Table 2).

Analgesic Requirements

At baseline, eight patients (40%) were on three or more analgesic agents (Table 1). Twenty-five percent of patients (N = 5) were taking analgesic agents more often than they were prescribed by their doctor, and 40% (N = 8) felt they were taking too many painkillers. The median pre-treatment morphine equivalent dose was 150 mg/24 hours (IQR 50,250). At 12 weeks post-treatment, three patients had a requirement for strong opiates. Four patients (20%) were on three or more analgesic agents. The median morphine equivalent dose at 12 weeks following treatment was 75 mg/24 hours (IQR 0, 150). This was a statistically significant reduction from baseline ($P < 0.01$). At baseline, 10 patients (50%)

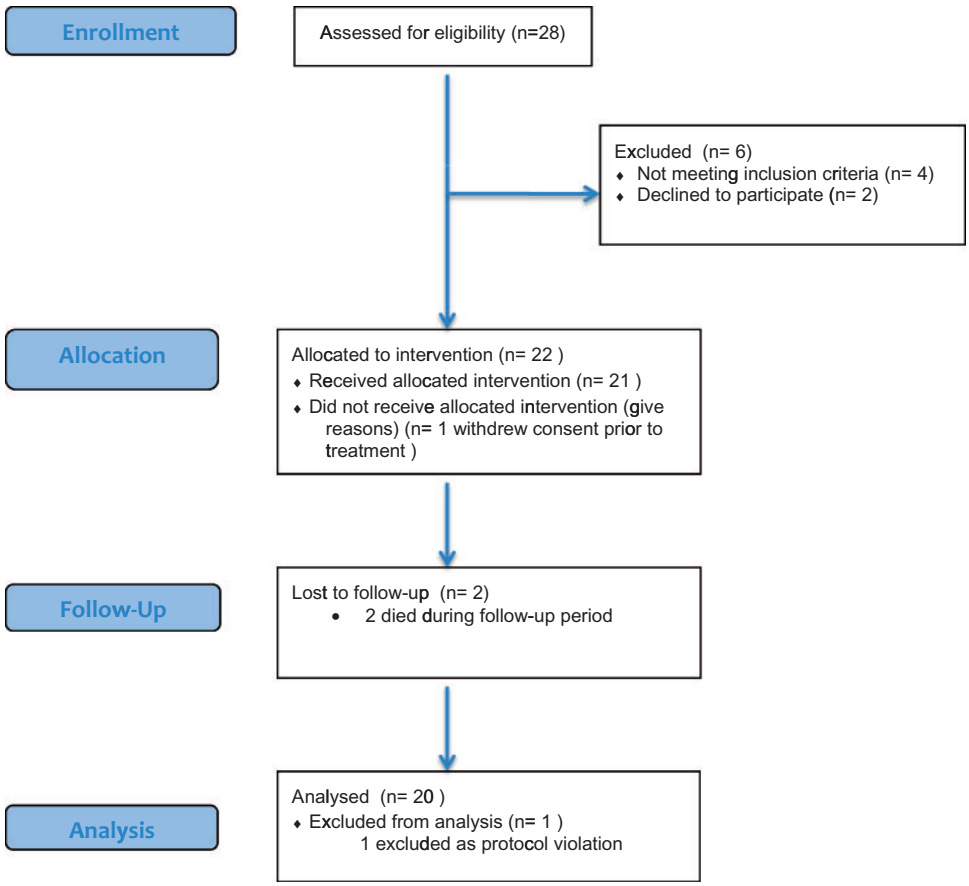

Figure 1 Flow diagram describing the number of patients screened, recruited, treated and followed-up.

Table 1 Basic patient demographics of those treated with Qutenza®

Sex (% age male)	55% (N = 11)
Age (years)	60 (13.9)
Indications for treatment	
Potentially remediable large vessel disease	5% (N = 1)
Irremediable small vessel disease	75% (N = 15)
Steal syndrome (from vascular access)	20% (N = 4)
Diabetes	20% (N = 4)
Previous myocardial infarction	25% (N = 5)
Pre-treatment BP (mmHg)	
Systolic	134 (17.9)
Diastolic	75 (16.2)
Analgesia at time of treatment	
Paracetamol	55% (N = 11)
NSAIDs	5% (N = 1)
Adjuvant agents	35% (N = 7)
Weak opiate	30% (N = 6)
Strong opiate	35% (N = 7)
Number of patients taking > 3 analgesic agents	40% (N = 8)
Median morphine equivalent dose (mg/24 hours)	150 (IQR 50, 250)

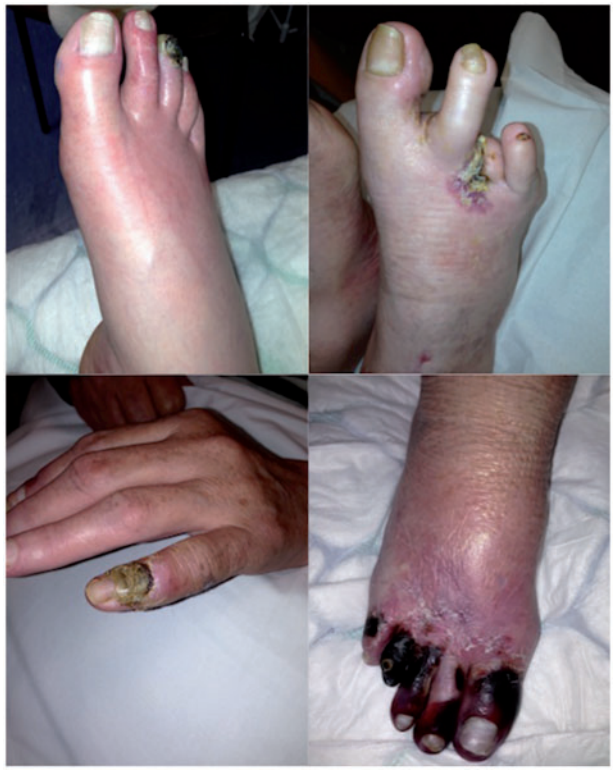

Figure 2 Right foot of 62-year-old man (top left) with ESRD secondary to adult polycystic kidney disease for over 30 years duration. He had critical ischemia affecting both feet with severe neuropathic pain, skin thinning and evidence of tissue loss. Following Qutenza® treatment his opiate requirements reduced by 50%. He went on to have revascularization of his leg with a femoral-distal bypass and amputation of his third and fourth toes for wet gangrene (top right). All of the post-surgical wounds (including those in the Qutenza® treatment field) healed well. Bottom left: Dry gangrene affecting fifth finger of left hand of 71-year-old lady following steal syndrome (high-flow fistula on the background of diabetic small vessel disease). Following ligation of the fistula, the pain persisted and her fingers were treated with Qutenza®. She had minimal response to treatment. Bottom right: Ischemic forefoot of 68-year-old woman who refused below knee amputation in favour of palliation. She had very poor pain control and suffered significantly from opiate toxicity, including a respiratory arrest. Following Qutenza® treatment she reported 50% reduction in pain scores and had a significant reduction in opiate requirements. She died 8 days following treatment.

complained of one or more side effects from analgesic agents. These included constipation (N = 7), drowsiness (N = 7), hallucinations (N = 3) and nausea and vomiting (N = 1). One patient had had a recent respiratory arrest secondary to opiate toxicity. Twelve weeks following Qutenza® treatment only three patients reported side effects from analgesic agents (constipation [N = 2], drowsiness [N = 1]).

Quality of Life

Median EQ-5D quality of life scores at baseline were as follows: mobility = 3 (IQR 2,4); self-care = 2 (IQR 1,3); usual activities = 3 (IQR 2,4); anxiety/depression = 2 (IQR 2,4); pain = 4 (IQR 2,5). There was a significant reduction in two domains of the EQ-5D score at 12 weeks: mobility = 1 (IQR 1,2) ($P < 0.01$); and pain = 2 (IQR 1,3) ($P < 0.01$). There was no significant difference in the other three domains of the EQ-5D score following treatment (Table 3).

Patient Global Impression of Change

Median PGIC scores at 12 weeks were as follows: activity limitations = 4 (somewhat better but the change has not made a significant difference) (IQR 2,6); symptoms = 6 (better, a definite improvement that has made a real worthwhile difference) (IQR 4,6); emotions = 4 (IQR 3,4); overall quality of life = 5 (moderately better, a slight but noticeable change) (IQR 4,6).

Safety and Adverse Events

The Qutenza® application was generally well tolerated as described above. Two patients died during the

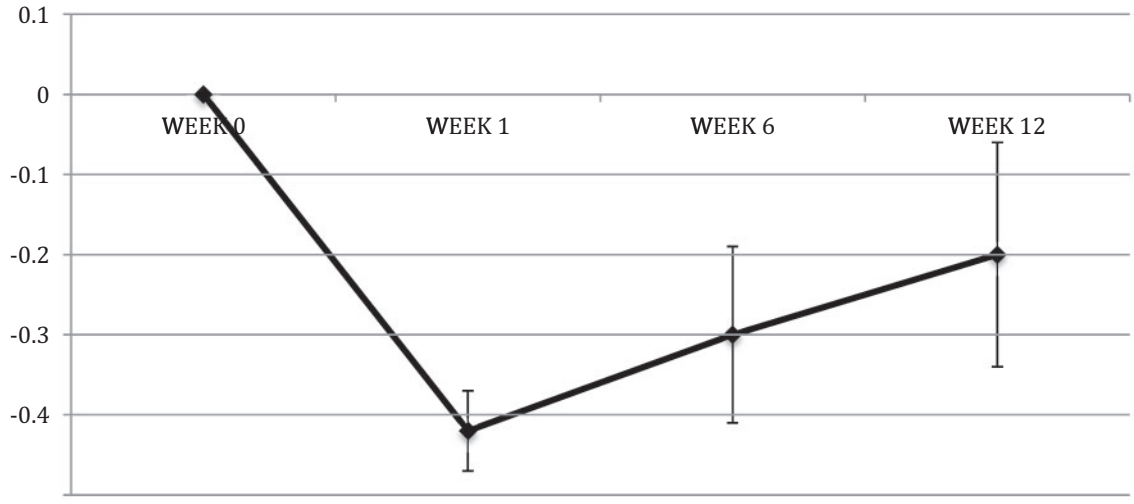

Figure 3 Mean percentage reduction in VAS from baseline at weeks 0, 1, 6 and 12. Error bars reflect 2 SD.

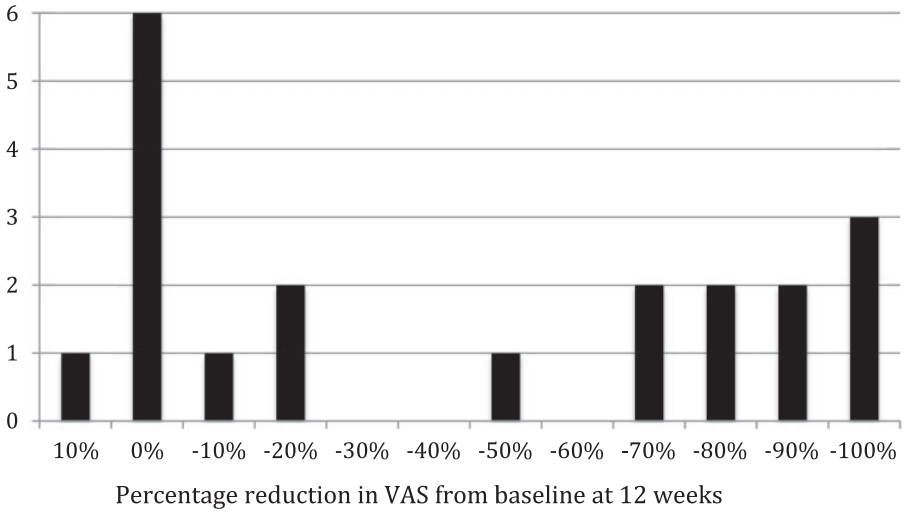

Figure 4 Frequency table outlining the number of patients reporting each percentage reduction in VAS from baseline at 12 weeks. This demonstrates the bimodal distribution in response to treatment with most patients either have a significant reduction in pain or no response to treatment.

12-week follow-up period (one myocardial infarction week 7, one from critical limb ischemia 8 days after treatment in a patient who was being managed palliatively and death expected prior to treatment). One patient had a cerebrovascular accident week 5 after treatment. Two patients required amputation for progressive disease (one below knee amputation [original treatment area had been distal to the level of amputation]; one toes [toes had been included in the treatment area]). One patient underwent a successful femoral artery-crural vessel bypass 8 weeks following Qutenza® treatment. It is not believed that any of these side effects related to the Qutenza® treatment, rather the underlying arterial disease.

Discussion

This small observational study is the first to use Qutenza® to treat patients with either ESRD or critical ischemia. We have demonstrated that Qutenza® is a safe and effective treatment for chronic neuropathic pain from critical ischemia in patients with ESRD with a 20% reduction from baseline in VAS at 12 weeks following treatment. We have also shown an improvement in BPI scores and in quality of life.

Chronic pain in patients with ESRD is common, with half of patients on hemodialysis reporting pain most days [21,22]; 74.8% of these patients stated that their

Table 2 Brief pain inventory score for each of the seven domains at weeks 0, 6 and 12. Data reflect median and IQR (interquartile range)

	Week 0	Week 6	Week 12	*P* value*
General activity	8 (IQR 4,9)	5 (IQR 3,6)	5 (IQR 3,6)	<0.01
Mood	7 (IQR 5,8)	4 (IQR 4,6)	4 (IQR 4,6)	<0.01
Walking ability	4 (IQR 4,7)	2 (IQR 1,5)	1 (IQR 1,6)	0.03
Work	3 (IQR 3,4)	2 (IQR 2,4)	1 (IQR 1,3)	0.04
Relationships	6 (IQR 3,8)	4 (IQR 3,6)	4 (IQR 3,6)	<0.01
Sleep	8 (IQR 4,9)	4 (IQR 2,5)	4 (IQR 2,5)	<0.01
Enjoyment of life	9 (IQR 8,9)	5 (IQR 3,7)	5 (IQR 3,7)	<0.001

**P* value compares week 0 and week 12.

Table 3 Quality of life scores for each of the five domains of the EQ-5Q questionnaire at weeks 0, 6 and 12. Data reflect median and IQR (interquartile range)

	Week 0	Week 6	Week 12	*P* value*
Mobility	3 (IQR 2,4)	1 (IQR 1,3)	1 (IQR 1,2)	<0.01
Self-care	2 (IQR 1,3)	1 (IQR 1,2)	1 (IQR 1,2)	N.S.
Usual activities	3 (IQR 2,4)	2 (IQR 2,4)	2 (IQR 2,4)	N.S.
Anxiety/depression	2 (IQR 2,4)	2 (IQR 2,4)	2 (IQR 2,4)	N.S.
Pain	4 (IQR 2,5)	2 (IQR 1,3)	2 (IQR 1,3)	<0.01

N.S. = non-significant.
**P* value compares week 0 and week 12.

pain was inadequately treated [22]. The World Health Organization (WHO) analgesic ladder can be used to treat chronic pain in patients with ESRD to some effect [23,24] but opiate side effects are much more common [23] and there is no evidence for adjuvants agents in this patient cohort [25]. In fact, there is very little evidence for any non-opiate analgesia in patients with ESRD. As a result, more than 10% of patients on hemodialysis regularly require strong opiate analgesia and a quarter of patients routinely take weak opiates [26]. As previously highlighted, a drug, such as Qutenza®, that is not renally excreted, has minimal systemic absorption, and does not require dose adjustment in renal failure is an attractive treatment option for these patients. We have found it to be safe, well-tolerated and an effective means of reducing opiate requirements in one of the first studies of non-opiate analgesia in patients with ESRD. In particular, the safety in diabetic patients, in whom Qutenza® was not licensed for use at the time of this study, is highlighted.

Qutenza® is currently licensed "for the treatment of neuropathic pain in non-diabetic adults" [27]. Twenty percent of the patients treated in this study were diabetic. The concern around treating diabetics with Qutenza® relates to a theoretical risk of non-healing blisters after application of the drug. Data from the early clinical trials [7,8,28] suggested that Qutenza® was safe in diabetics and there was no difference in the incidence of local side effects experienced by diabetics and non-diabetics [9]; however, the number of diabetic patients in these studies was small and this was certainly a concern shared by us prior to the study. Patients with critical ischemia (especially diabetics) have particularly fragile, vulnerable skin, which is often erythematous, thinned and shiny (Figure 2). Due to the poor blood supply, any injury to this skin can result in non-healing ulcers and may ultimately lead to amputation. However, given that a significant proportion of patients with ESRD and PVD were also diabetic, we felt it essential to include this patient group in the study. We did not observe any significant complications associated with erythema or blistering. Treatment was well-tolerated in both diabetic and non-diabetic patients (including those with areas of ulceration, which we simply treated around).

Several of the patients in this study are likely to have had an element of painful diabetic neuropathy (without sensory loss) overlapping with the pain from critical ischemia, as it is very difficult to make the distinction clinically between the two and, in reality, they often coexist. This interrelationship risks confounding results; however, it is typical of what is observed in "real life"

clinical practice. Furthermore, Webster et al. (2011) [29] demonstrated that Qutenza® was effective in treating painful diabetic neuropathy with a 31.5% reduction in mean pain scores at 2–12 weeks post-treatment in 91 patients. This level of response is comparable to that observed in the studies of gabapentin in diabetics [30,31] and Qutenza® treatment avoids the systemic side effects (especially drowsiness) observed in the other adjuvant studies [28].

Within our patient cohort, we observed a bimodal distribution in response to Qutenza® treatment, with patients either having little or no response or a near complete response. Thirty-five percent ($N = 7$) had no response to treatment, while 45% of patients had a reduction in pain score $>$ 65% at 12 weeks. Martini and colleagues (2012) describe a similar pattern of response [32]. In their cohort of 91 diabetic patients, they report four groups of patients with distinct clinical response (worsening pain, no response, short-lived response, persisting maintained response); however, like we observed, the majority of patients either had no or near complete response. We did not observe patients with a transient response to treatment and hypothesize that this may be a result of resolution of the underlying pathology that caused the neuropathic pain prior to treatment in our cohort (i.e., patients who had persistent pain after ligation of a fistula for steal syndrome, had an excellent and long-lasting response to treatment as the original insult which caused the pain had been removed before initiation of treatment). To date, only short duration of symptoms prior to treatment has been predictive of good response to Qutenza® [12,33]. Further work will help identify other predictors of response and may help target treatment in the future.

All patients in this study were pre-treated with EMLA cream as was standard practice at the time the study began. Recent work from Germany indicates that it is possible to use Qutenza® without prior treatment with a topical local anesthetic [34] and there is a growing body of anecdotal evidence to support this [35]. Patients with ESRD and critical ischemia are particularly fragile and vulnerable. We would not currently advocate treating these patients without prior treatment with a topical local anesthetic.

This is a small, observational study with no comparator group. The patient cohort is heterogenous but is representative of clinical practice. Intentionally broad inclusion criteria mean that the results of this study are generalizable across the range of patients (including diabetics) encountered in everyday practice. Small patient numbers risk type 2 error and these results will need to be confirmed within a larger cohort. However the magnitude of response observed is biologically plausible and comparable to that seen in other patient group [7,10]. Furthermore, we have confirmed safety and tolerability in this vulnerable patient cohort.

Conclusion

In conclusion, we have demonstrated that Qutenza® is a safe and effective treatment for the chronic neuropathic pain of critical ischemia in patients with ESRD. Minimal systemic absorption, lack of renal excretion and avoidance of need to dose adjust in renal failure make it an attractive option to treat this otherwise difficult to manage condition.

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