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Ziconotide for spinal cord injury-related pain

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Abstract

Background: Central neuropathic pain related to spinal cord injury is notoriously difficult to treat. So far most pharmacological and surgical options have shown but poor results. Recently ziconotide has been approved for use both neuropathic and non-neuropathic pain. In this cohort study, we assessed responder rate and long-term efficacy of intrathecal ziconotide in patients with pain related to spinal cord injury.

Methods: Patients presenting chronic neuropathic related to spinal cord lesions that was refractory to medical pain management were considered for inclusion. Those accepting were tested by lumbar puncture injection of ziconotide or continuous intrathecal infusion and if a significant decrease in pain scores (>40%) was noted they were implanted with a continuous infusion pump. They were then followed up for at least 1 year with constant assessment of the evolution of pain and side effects.

Results: Out of the 20 patients tested 14 had a decrease in pain scores of more than 40% but only 11 (55%) were implanted with permanent pumps due to side effects and patient choice. These were followed up on average for 3.59 years (±1.94) and in eight patients an above threshold decrease in pain scores was maintained. Overall in patients that responded to the test baseline VAS was 7.91 and 4.31 at last follow-up with an average dose of 7.2 μg of ziconotide per day. Six patients (30%) did not respond to any test and in three patients side effects precluded pump implantation. No significant long-term effects of the molecule were noted.

Conclusion: This study shows response to intrathecal ziconotide test in 40% of the patients of a very specific population in whom other therapeutic options are not available. This data justifies the development further studies such as a long-term randomized controlled trial.

Significance: Intrathecal Ziconotide is a posible alternative for the treatment of pain in patients with spinal cord injury and below level neuropathic pain.

1 | INTRODUCTION

Spinal cord lesions as is the case for most severe injuries of the somatosensory system, lead to a high prevalence of neuropathic pain that may range from 40% to 96%, with severe and disabling pain in up to 50% of patients (Dijkers, Bryce, & Zanca, 2009; Siddall, McClelland, Rutkowski, & Cousins, 2003).

Treatment of this type of central neuropathic pain is challenging and both pharmacologic therapies and non-pharmacological therapies are rarely effective as was recently reviewed (Boldt et al., 2014). Surgical techniques such as

neuromodulation (spinal cord stimulation) and lesioning techniques (DREZ lesion) have also been tried with poor results (Moreno-Duarte et al., 2014; Sindou, Mertens, & Wael, 2001).

Chemical neuromodulation in these patients, especially intrathecal morphine has had controversial long-term results (Anderson & Burchiel, 1999; Thimineur, Kravitz, & Vodapally, 2004) somewhat limiting its use in current practice. However, since 2004 and 2005 the Food and Drug Administration (FDA) and European Medicines Agency (EMA) respectively have approved the use of ziconotide for neuropathic pain making it a candidate for the treatment of pain related to SCI (Rauck, Wallace, Burton, Kapural, & North, 2009).

Ziconotide acts by binding to N-type Calcium channels situated on the terminal part of primary afferent neurons of the nociceptive pathway (Baddack et al., 2015) therefore reducing synaptic transmission (Bourinet et al., 2014) with potent antinociceptive effects (Wang, Pettus, Gao, Phillips, & Scott Bowersox, 2000). Distribution of these calcium channels in humans is not restricted to the spinal cord, they can also be found in the brain, suggesting the possibility of additional supramedullary effects (Zamponi, Striessnig, Koschak, & Dolphin, 2015).

Human studies have shown the efficacy of ziconotide for the treatment of various types of chronic pain (Deer et al., 2018) most notably in three randomized controlled studies with short-term follow-up (Rauck et al., 2006; Staats et al., 2004; Wallace et al., 2006). In a review of the treatment of neuropathic pain by ziconotide the necessity for further studies on more clinically homogenous groups was pointed out (Rauck et al., 2009). Particularly information on the efficacy of ziconotide on central neuropathic pain is, for now, unavailable. Given the lack of alternative efficient therapeutic methods for pharmaco-resistant neuropathic pain related to SCI, ziconotide is an attractive option.

This pilot study was constructed as a prospective cohort to provide data regarding the interest and feasibility of potential future randomized controlled trial on ziconotide for the treatment of SCI-related neuropathic pain. Our main objective was to estimate the proportion of patients with SCI-related pain that may be responders to intrathecal ziconotide (ITZ) tests and asses the long-term stability of the tested response.

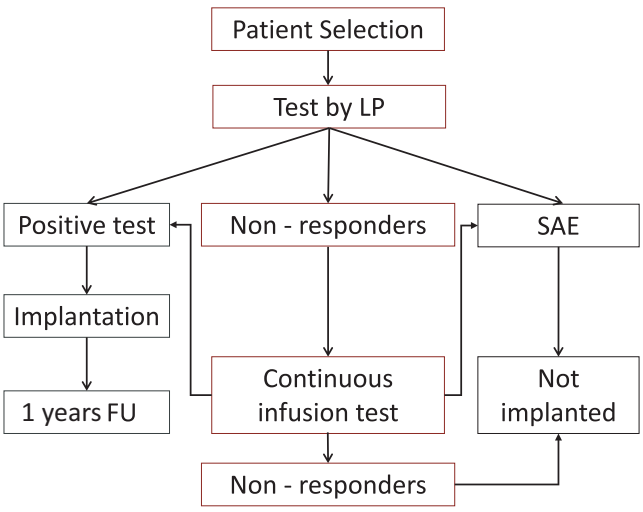

FIGURE 1 Flow chart of the study design

2 | METHODS

2.1 | Study design

This study was designed to test a prospective cohort of patients with definite central neuropathic pain as defined by the IASP criteria (Treede et al., 2008) related to SCI, refractory to conventional pharmaco-therapy of NP, and treated by continuous intrathecal ziconotide (ITZ). The study had five steps: (a) initial selection of patients; (b) a period of stabilization of oral analgesic medication; (c) a test period either although lumbar puncture or (if negative or impossible), by continuous infusion via an implanted subarachoid catheter and reservoir; (d) in responders, continuous long-term treatment through an implanted pump, and (e) assessment of efficacy in the long term. Figure 1 gives the outline of the study design and Table 1 gives detailed inclusion and exclusion criteria.

TABLE 1 Inclusion and non-inclusion criteria

Inclusion criteria:
1. Patient >18 year old
2. Patients with stabilized spinal cord lesion
3. Patients with refractory neuropathic pain (failure to opioids or at least two class of antineuropathic pain drugs)
4. Experiences pain ≥5/10 on numeric scale
5. Patients with a positive trial test to Ziconotide either by lumbar puncture or by continuous infusion above the lesion via an implanted catheter
6. Evaluation performed by a multidisciplinary team in a pain centre
7. Patients eligible to implantation of a subcutaneous pump
8. Signed informed consent
9. Patients benefiting from a social insurance system or a similar system
Non-inclusion criteria:
1. Life expectancy <5 years
2. Suffering from other neuropathic pain or chronic pain due to cancer
3. Being treated with spinal cord stimulation, nerve stimulation, intrathecal analgesic delivery system with analgesic drug (except Baclofen) until the last 6 months
4. Implant ITZ surgery contraindication (MRI or anaesthesia contraindication coagulation disorder, immune depression, Current infection, Critical respiratory and Heart illness)
5. Unable to operate the ITZ equipment or comply with study requirements
6. Suspicion of substance abuse
7. Current or planned pregnancy
8. Patient unable to understand the purpose of the trial
9. Participation to another trial that would interfere with this trial
10. Patients under legal protection

TABLE 2 Demographics and pain characteristics

ID	Sex	Age	Aetiology	NLI	Base VAS	At Level VAS	Below Level VAS	Paroxystic VAS	Continuous VAS
1	M	59	Trauma	L2	7	7	0	0	7
2	F	53	Tumour	C7	9	10	7	10	7
3	M	30	Trauma	T6	6	0	7	0	7
4	M	56	Ischemia	L2	8	8	8	8	8
5	F	59	Trauma	C6	8	0	8	8	8
6	M	33	Trauma	T1	8	0	8	0	8
7	M	54	Trauma	T5	5	0	7	0	7
8	F	56	Trauma	C7	7.5	0	8	0	8
9	M	36	Trauma	T7	8	0	8	8	5
10	F	49	Syringomyelia	T8	8	8	0	0	8
11	M	42	Syringomyelia	C2	7	7	0	0	7
12	F	57	Trauma	T4	9	9	4	9	4
13	M	71	Trauma	T4	7	0	7	0	7
14	M	46	Trauma	T12	9	9	0	9	0
15	M	42	Ischemia	L1	9	9	0	9	0
16	M	72	Trauma	T10	9	9	2	9	2
17	M	39	Tumour	T5	8	0	8	0	8
18	M	48	Trauma	C6	6	0	6	0	6
19	M	45	Trauma	T12	8	9	8	9	8
20	M	32	Trauma	T6	7	7	7	7	7

2.2 | Study endpoints

2.2.1 | The primary endpoint was the proportion of patients responders to the ITZ tests

Patients were considered as responders if they reported a reduction of VAS greater than or equal to 40%.

Secondary endpoints were the assessment of long-term efficacy (change in VAS), impact on different features of pain and changes in analgesic medications.

2.3 | Step 1: Patient selection and assessment

Twenty consecutive patients were recruited by a single university pain treatment clinic (pain centre of the Neurology and Neurosurgery Hospital of Lyon). Selected patients had pain related to a SCI either traumatic, postsurgical, ischemic or due to syrinogomyelia documented by clinical, imaging and when necessary electrophysiological testing. Specific aetiologies for all patients and demographics are found in Table 2. At the inclusion visit patients were examined to determine the NLI, the neuropathic nature of the pain, its features (continuous and/or paroxysmal) and territory of distribution distinguishing between at-level pain and below level pain as defined by the international SCI pain classification (Bryce, Biering-Sørensen, et al., 2012; Bryce, Ivan, & Dijkers, 2012).

Prior treatment was reviewed to verify the refractory nature of the pain. Pain was defined as refectory if two different classes of medication have been used both alone and in association at doses above the recommended dose and at the maximum level of tolerability for at least 3 months and when applicable spinal cord stimulation had been tested (Attal et al., 2010; Moreno-Duarte et al., 2014).

ITZ is approved as analgesic therapy for refractory chronic pain including neuropathic pain by the French National Authority for Health (Haute Autorité de Santé see Appendix S1) since 2008 based on the previous randomized trials (Rauck et al., 2006; Staats et al., 2004; Wallace et al., 2006). At the inclusion visit, as for all patients submitted to intrathecal infusion of analgesics, patients signed an informed consent describing in details the benefits/risk ratio of the therapy.

2.4 | Step 2: Stabilization of medication

After inclusion and written informed consent patients entered a 30-day stabilization period in which oral treatment for pain was maintained at an optimal level. This was carried on throughout the test period.

2.5 | Step 3: Initial test

At admission for the initial test pain intensity scores were assessed. Average VAS over one week prior to the test was recorded as well as VAS just prior to the tests. This was considered the baseline for the test while the former as a baseline for long-term follow-up.

For all patients initial test was attempted via lumbar puncture (LP). However, in one patient in whom CSF flow was known to be altered the initial test was performed through the implantation of an intrathecal catheter placed above the spinal lesion and connected to a subcutaneous port.

2.6 | LP test

Three consecutive LPs were performed at a 72-hr intervals, to administer ziconotide boluses at progressively increasing dosages of 0.5, 1.0 and 1.5 μg diluted in 2 ml of saline. Patients were monitored for vital and neurological signs just before each LP, every hour for the first 24 hr after LP and then every 4 hr for the subsequent 24 hr. Biological data including creatine phosphokinase and creatinine were measured 24 hr after the first LP and at the end of LP test period. The ward nurse assessed thereafter VAS and adverse effects (see Table 3) during each visit (just before the LP and 1 hr, 4, 8, 12, 24 and 48 hr after the LP). After 24 hr patients were asked to grade their degree of pain reduction from 0% to 100%. Patients satisfaction with the therapy was also evaluated using item 5 of the Participant Satisfaction Reporting Scale (0 – no satisfaction with the therapy, 100 complete satisfaction with the therapy. (Riley et al., 1999).

Patients were considered "responders" if they had reduction of VAS greater than or equal to 40% or if they declared a degree of satisfaction of more or equal to 40%. Responders to the LP test were implanted with a continuous infusion pump. Patients having severe adverse effects (AEs) during the test period were not implanted with a permanent pump as well as patients not desiring the therapy.

2.7 | Continuous infusion test

In patients in whom the LP test was not successful a continuous infusion test was performed by means an intrathecal catheter connected to a subcutaneous small reservoir (see below for technique). An external pump (Cane Crono 5 Infusion Pump, Applied Medical Technology, Italy) was connected to the sub cutaneous site via a HUBER needle. Then a continuous infusion was performed at dosage from 2 to 10 μg maximum per day with an increment of 1 μg every 3 days. Pain was evaluated every 4 hr for the VAS and every day for the degree of satisfaction. As for LP test patients were considered responders if they declared a reduction of VAS greater than or equal to 40% or if they declared a degree of satisfaction of more or equal to 40%.

2.8 | Step 4: Catheter and Pump implantation

Before intrathecal infusion testing, the subarachnoidal space was checked for absence of CSF blockage by T2 MRI sequences of the entire spinal or by myelography. The patients in whom CSF blockage was present were all post traumatic cases. For these patients, the intrathecal catheter was implanted above the lesional level. In all other patients, the catheter was implanted in the lumbar region with the tip facing the conus medularis whatever be the lesional level.

Lumbar catheters were implanted using a percutaneous technique with TUOHY needle. The position of the tip was verified by intraoperative radiology. In case of blockage, supralesional catheter were placed surgically trough an interlaminary approach. A midline incision of the dura was performed and the catheter was passed in cranial direction with the tip placed two or three vertebral levels above the lesional level. A circular suture was made to fix the catheter to the dura and ensure watertight closure. An subcutaneous reservoir was placed in the abdominal region (usually on the left flank) and connected to the catheter after checking the CSF flow.

Permanent, subcutaneous continuous infusion pumps were implanted in cases were LP tests or continuous infusion tests were positive. In all cases a Syncromed II pump by Medtronic Inc., WI, USA was implanted. Both the 20 ml (ref 8,637) and the 40 ml (ref 8,637) pumps were used according to the dosage used during testing and patient morphology. In cases of positive bolus tests the pump was implanted in the same surgical session as the catheter.

In patients in whom continuous infusion test was performed, the pump was implanted in the same site as the subcutaneous reservoir used for the trial. This was performed two weeks after the end of the test, so as to prevent infection.

2.9 | Step 5: Long-term therapy (drug administration) and follow-up

Patients with an implanted pump were seen in the outpatient clinic initially at one month and then every 6 weeks for assessment and pump refill. VAS score was assessed at each visit (at 1, 3, 6, 8, 12 months and last FU) as well as VAS score over the past 3 days. Patients were questioned for AEs. Values of CPK were measured before each outpatient visit and the value was considered when increasing doses. Dose increases, if necessary, were performed in increments of 0.5 μg per visit. A maximum theoretical limit was imposed at 20 μg/day as recommended by the HAS.

TABLE 3 Test results in each patient

Patient	LP test result	SAE	CI test result	SAE	Implanted	VAS Base	VAS last FU	Delta	Dose per day	Follow-up
1	POS		NP		Yes	7	6	−14.3	7 μg	5.34 year
2	POS		NP		Yes	9	5	−44.4	4 μg	4.75 year
3	POS		NP		Yes	6	0	−100	6.9 μg	5.28 year
4	POS		NP		Yes	8	5	−37.5	1.99 μg	5.4 year
5	POS	CPK	NP		No					
6	NEG		POS	Infection	Yes	8	7	−12.5	17 μg	4.9 year
7	NEG		NP		No					
8	POS	AUR	NP		No					
9	NEG		NEG		No					
10	POS		NP		Yes	8	5	−37.5	2.5 μg	1.1 year
11	POS		NP		Yes	7	6.5	−7.1	2.5 μg	3.15 year
12	NEG		NEG		No					
13	NEG		POS		Yes	7	2	−71.4	5.72 μg	1.67 year
14	NEG		POS		Yes	9	4	−55.5	3.2 μg	1.48 year
15	POS		NP		Yes	9	5	−44.4	3.5 μg	5.4 year
16	NP		POS		Yes	9	2	−77.8	3.5 μg	1 year
17	NEG		NEG		No					
18	NEG		NEG		No					
19	POS	CPK	NP		No					
20	NEG		NEG		No					
						7.9 ± 1.04	4.31 ± 2.14	−45.7 ± 29.7	5.36 μg	3.59 ± 1.94 year

Abbreviations: POS, Positive; NEG, Negative; NP, Not Performed.

2.10 | Statistical analysis

Categorical variables were expressed as number (n) and percentage and quantitative variables were expressed as median and minimum and maximum as the sample was small.

Pain scale evaluation was compared between follow-up steps using nonparametric test of Wilcoxon as the hypothesis of normality of distribution was not verified. The initial statistical tests were bilateral and the level of significance was set to 5% ($p < 0.05$) but to account for multiple comparison, Bonferronni's correction was applied and the p value was set to 0.0025. Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., NC, USA).

3 | RESULTS

3.1 | Permanent pump implantation

A total of 20 patients participated and 14 of these had an above threshold decrease in their pain scores and were considered responders to the test either by LP or continuous infusion. Of these only eleven were implanted due to severe adverse effects during testing in 3. Figure 2 and Table 3 summarize the patients' evolution according to responses to both the LP and continuous infusion test and final pump implantation. Patient satisfaction was not a decisive criterion for any of the patients considered responders since all patients satisfied the VAS decrease in 40%. Data on patient satisfaction are given in the online Tables S1 and S2.

3.2 | Evolution of pain

Patients who responded and were implanted with a permanent pump were followed up on average for 3.59 years (±1.94). In eight of these patients VAS score at the end of the follow-up period was with at least 3 points (3.5 on average) lower than at baseline (8.125 on average) in such a way that at last follow-up 72% of implanted patients maintained the 40% decrease observed during the testing period (58% on average). In three patients, this was not the case and they had a minimal benefit with an average decrease of VAS score of less than 1 point (11% on average). Individual pain scores at baselines and at the iterative follow-up visits are given in Figure 3.

Overall in patients that responded to the test baseline VAS was 7.91 and 4.31 at last follow-up. The absolute value of the average VAS significantly decreased between baseline and last follow-up with an average decrease in more than three points (45.5% $p = 0.02$ Wilcoxon rank sum test). At 1 month follow-up the mean VAS significantly decreased (3.4, 54.8% $p = 0.001$ Wilcoxon rank sum test). Evolution of average pain is illustrated in Figure 4.

3.3 | Results on pain features

Among the 20 patients in this study 11 (55%) had at level pain and 15 (75%) below level pain. Among the 14 patients that were considered responders about one third (5%–35.7%) had pain only at level, approximately another third (5%–35.7%) had only pain below the level of injury and a little less than one-third (4%–28.5%) had pain both at level and below the NLI. However, in the non-responder group ($n = 6$) all patients had pain below the NLI and only two had at level pain. No significant difference was noted between the responder and non-responder groups ($p = 0.3354$, Fisher exact test).

Among the 20 patients in this study, 10 (50%) had paroxystic pain and 18 (90%) continuous pain. In the responder group ($n = 14$) only two patients had exclusively paroxystic pain, whereas seven (50%) had exclusively continuous pain. The remaining five (35.7%) patients had both types of pain. However, in the non-responder group ($n = 6$) all patients had continuous pain and only three had paroxystic pain. No significant difference was noted between the responder and non-responder groups ($p = 1$, Fisher exact test).

At last follow-up the mean percentage of decrease in VAS score for paroxystic pain was 82.1%, whereas for the continuous pain was 32.7%.

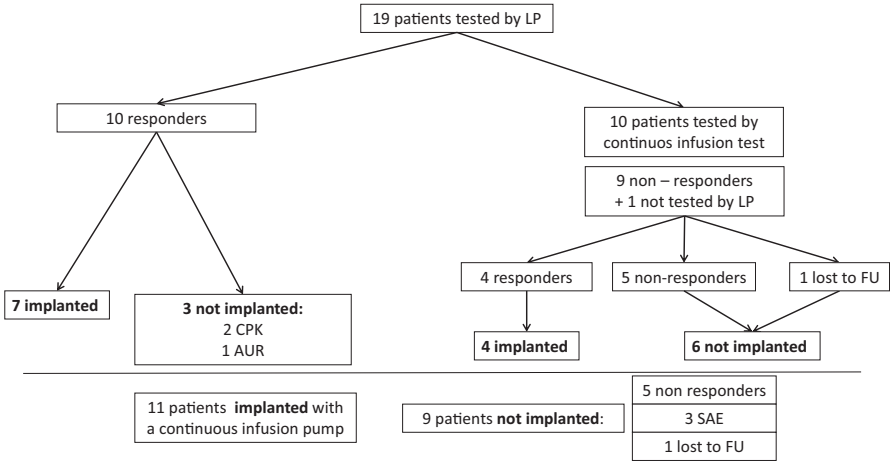

FIGURE 2 Outline of the responses to the lumbar puncture and continuous infusion tests

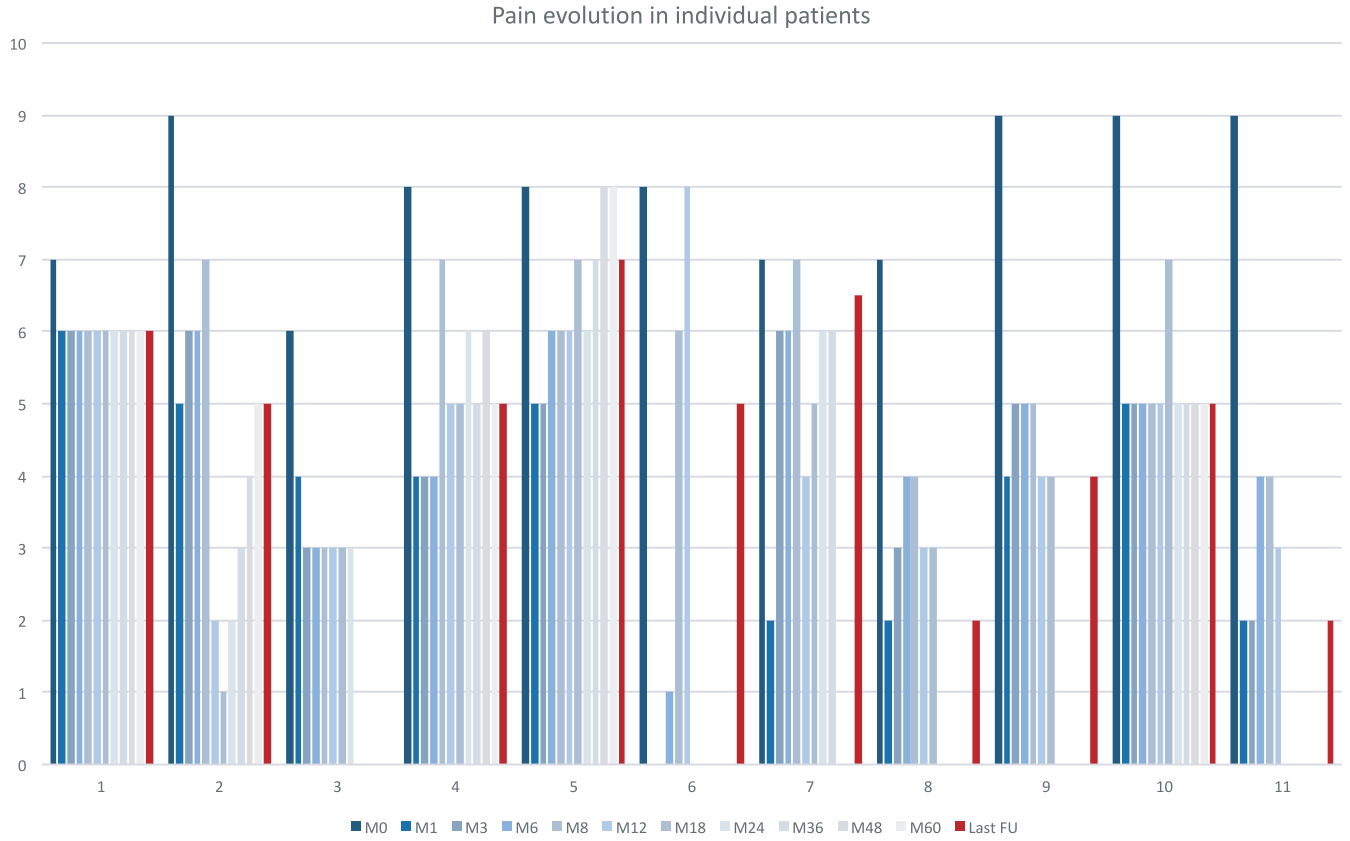

FIGURE 3 Individual pain scores at follow-up after pump implantation in the 11 patients receiving long-term treatment with ziconotide. VAS pain scores are given at baseline, 1 month after implantation next 3, 6, 8, 12, 18, 24, 36, 48, 60 and at last follow-up (3.59 years on average)

3.4 | Medication

In the initial population of 20 patients, 15 benefited from antiepileptic medications and out of the 11 implanted patients, 8 were treated with antiepileptics. At last follow-up, two patients had stopped completely this treatment. Similarly, out of the total population, 12 patients were treated with antidepressants, eight being in the implanted group. Two patients have completely stopped their antidepressant medication at last follow-up. These patients were the same as those having stopped their antiepileptic medication. Table 4 gives the comparison of medication taken before implantation and at last FU in patients that benefited from permanent pump implantation.

In the initial population 7 patients were treated with opioids with an average dose of 605 mg of morphine equivalents (60–3,600 eqmg). In the implanted group 4 patients were treated with opioids prior to the study. Two of them stopped completely their opioid medication and two decreased it by an average of 84%.

3.5 | Responses of pre-implantation test

Out of the 20 patients tested, 10 patients responded to the initial LP test and nine did not. One patient was not tested by LP due to CSF blockage on MRI and had a direct continuous infusion test and was considered a responder.

Among the 10 responders to the LP test, seven patients benefited from the implantation of a permanent pump. Three others had serious adverse event (SAE) preventing permanent pump implantation (two had important increase in CPK and one had acute urinary retention).

Nine patients benefited from a continuous infusion test. Out of the nine non responders to the LP testone was lost to follow-up before the continuous infusion test. An additional patient had the test without a prior LP test because of CSF flow obstruction on pretest MRI. Four responded to the test and benefited from a permanent pump implantation. Five patients did not respond and were not implanted.

Overall out of 20 patients tested 11 (55%) had a chronic treatment with ITZ by an implanted intrathecal infusion pump.

3.6 | Responses according to dosage

3.6.1 | Response to the LP test

After intrathecal injection of ziconotide via LP, first mean decrease in VAS was noted at 1 hr after the injection (decreasing from 7.2 prior to the test and 5.78 at 1 hr after

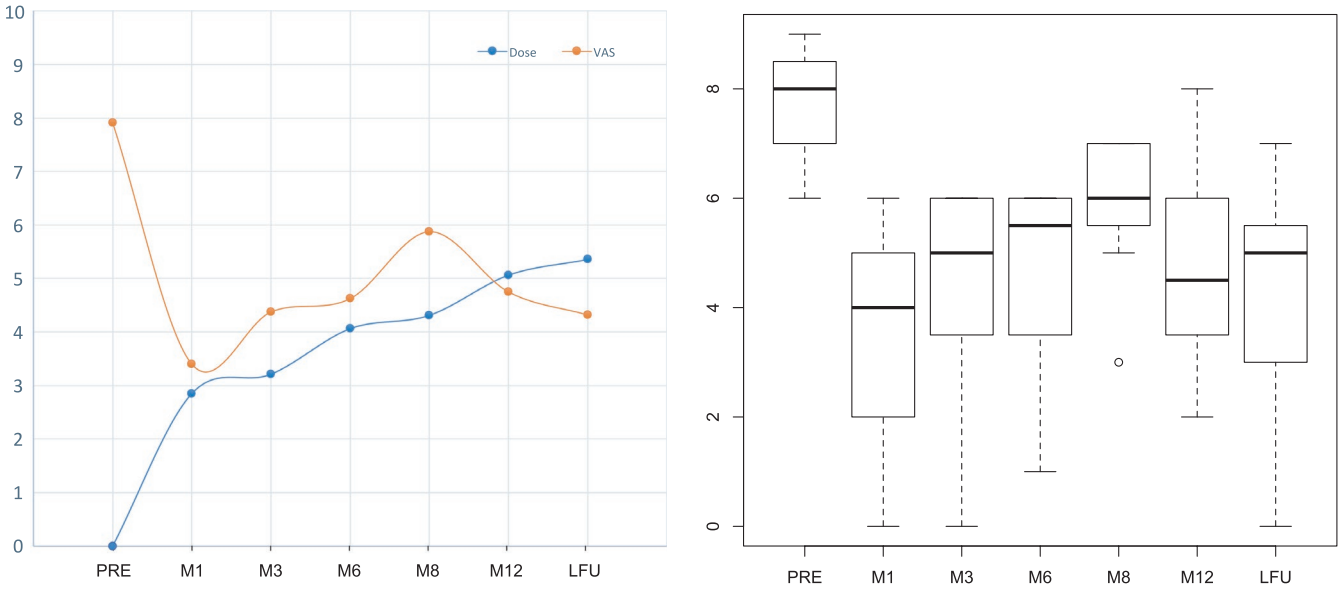

FIGURE 4 Evolution of VAS score compared to dose increases. On the left evolution of the dose of intrathecal ziconotide in relation to the average VAS score in the 11 implanted patients. On the right box plot of the evolution of pain scores with averages and confidence intervals in the same 11 patients

TABLE 4 Evolution of medication

	Pre test			One Year		
ID	OE (mg)	AE	AD	OE	AE	AD
1	3,600	No	No	600	No	No
2	0	Yes	Yes	0	Yes	Yes
3	0	Yes	No	0	Yes	No
4	180	Yes	No	0	Yes	No
6	0	Yes	Yes	0	Yes	Yes
10	0	No	Yes	0	No	Yes
11	120	Yes	Yes	20	No	No
13	0	No	Yes	0	No	Yes
14	100	Yes	Yes	0	No	No
15	0	Yes	Yes	0	Yes	Yes
16	0	Yes	Yes	0	Yes	Yes

Abbreviations: OE, opioid equivalents (mg); AE, Antiepileptics; AD, Antidepressants.

the test). This response was maintained constant until 12 hr after the initial injection as seen in Figure 4a. At 24 hr after the initial injection no decrease in VAS score was observed (VAS – H24: 6.9). Whatever the dose used, the profile of the response does not seems different (see Figure 4b). However response to a small dose (1 μg) seems reduced when compared to 1.5 and 2 μg, respectively. Maintenance of the response over the 12-hr period seems to be more constant with the higher dosage (2 μg). This needs to be confirmed over a larger sample.

3.6.2 | Evolution of the response throughout the follow-up period

After pump implantation, we noted a significant decrease in VAS noted at 1 month as detailed above. Over the follow-up period the dose of ziconotide constantly increased on average. At 1 month after implantation average dose was 2.85 μg per day whereas this was 5.44 at last follow-up. Pain scores evolved in parallel but did not stabilize until 1 year after pump implantation. This is shown in Figure 4.

3.6.3 | Side effects and complications

During the test period three patients experienced complications related to the product. All complications happened after LP tests. Two patients experienced severe increases in serum CPK (above 3,000 μg/L) and testing was halted. Both patients had their increase in CPK after the second dose of ziconotide and were considered test responders in relation to their pain decrease after the ITZ injection. They did not experience any further severe complications. One patient experienced acute urinary retention at the dose of 2 μg LP test dose and although had experienced a significant improvement in pain did not desire to continue with a CI test that had been proposed.

One of the patients implanted with an IT catheter had a surgical site infection with meningitis requiring removal of the catheter. Antibiotic treatment lead to complete resolution of the infections episode and he was afterwards reimplanted for a CI test that proved to be positive and was implanted with a

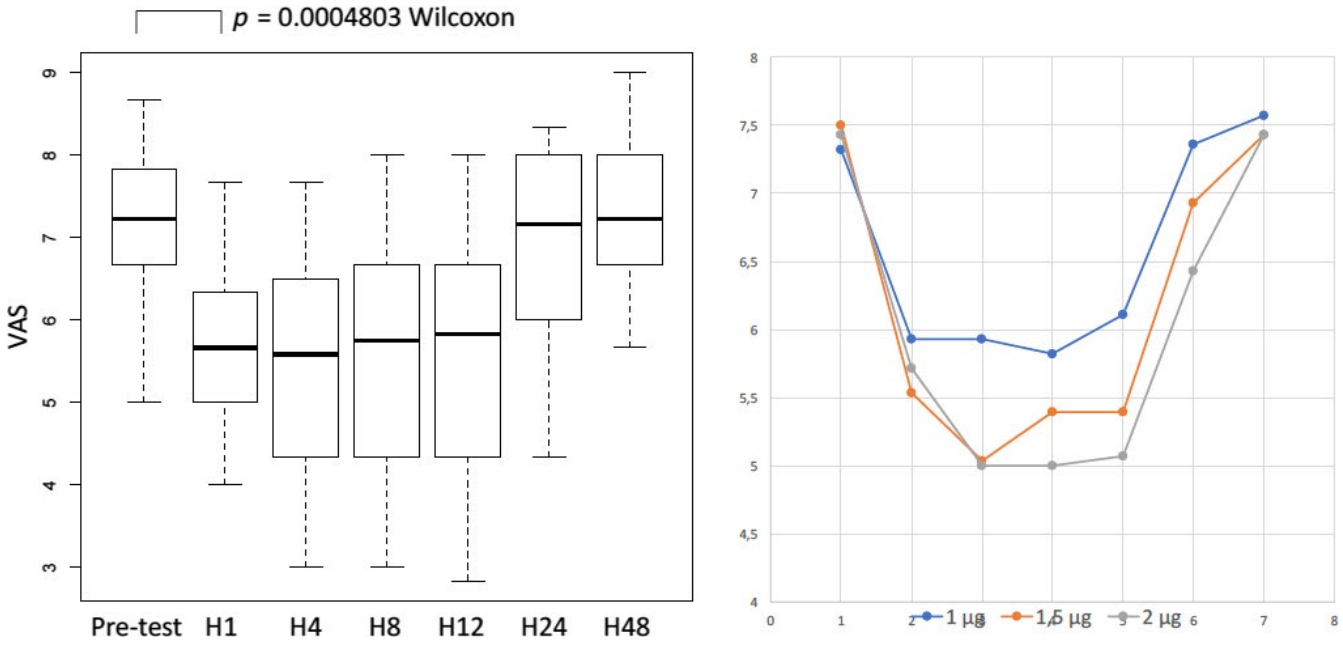

FIGURE 5 Pain scores during the first 48 hr after lumbar puncture test. On the left boxplot of averages of the three doses used in 19 patients at distinct moments: immediately pretest and after the test at 1, 4, 8, 12, 24 and 48 hr. On the right average pain scores, according to the dose used in the lumbar puncture test at the same time intervals as on the right

permanent pump. Yet another patient that did not respond to the LP test or the CI test a self-resolving pseudomeningocele at 1 month after the surgical implantation of the catheter was noted.

After the test period and pump implantation in three patients' minor increases in CPK levels have been noted (below 300 µg/L). These did not prompt to any medical action (Figure 5).

4 | DISCUSSION

This study tests the efficacy of ziconotide on central neuropathic pain in patients with spinal cord injury both in a short- and a long-term settings. To our knowledge, it is the first study to explore efficacy of this molecule for such a specific homogenous group. Previous studies, particularly the randomized controlled trials have focused on large, diverse patient populations (Rauck et al., 2006; Staats et al., 2004; Wallace et al., 2006). It is also one of the studies with the longest follow-up in patients with chronic ITZ treatment. Furthermore, over half of the 20 patients group (55%) responded to the test and 40% (8 of 20) benefited from long-term treatment with a clinically significant impact on pain. This is of value given the lack of alternative treatments available for this type of pain (Boldt et al., 2014).

4.1 | Limitations

The main objective of the study was to assess the usefulness of further studies with intrathecal ziconotide for pain related to spinal cord injury pain by providing the proportion of patients responding to initial use of this therapy in a test setting. The choice of the proportion of responders as a primary outcome was made to be as informative as possible on the distribution of responses and thus characterize the treatment effect. This is in concordance with current recommendations (Dworkin et al., 2009).

We further followed these patients in an open label fashion to assess the long-term stability of the impact in pain. By design this study is self-limiting. Data on patient quality of life were not collected as this was never set into the design of the study. Simple VAS scores and their evolution are the main outcome measure. The results of the present study are therefore to be carefully interpreted. Intrathecal ziconotide may be a useful therapy for patients with spinal cord injury but this is not yet a validated therapy. The primary objective of the study, although achieved, cannot be a substitute for high level clinical evidence of efficacy. It is but a preliminary stage. In this sense a randomized controlled trial has been launched based on data obtained from this study.

Another important limitation of this study is its uncontrolled open label design. Further double blinded placebo controlled studies to confirm the long-term efficacy suggested by our study are needed and justified by this pilot study. The first positive results encourage such studies to further confirm the usefulness of ITZ in this indication.

A third limitation is the small size of population but this may be somewhat compensated by the homogeneity of the group that includes only patients with definite central

neuropathic pain related to spinal cord injury. Moreover, in the actual study the variance of the response in pain ratings to ITZ treatment is a relatively small at least in those patients that were responders. This allows the drawing of conclusions with some degree of reliability despite the small population.

The choice of using a 40% threshold as the cut-off for a positive test may also be a limitation in that it is a stringent criterion by comparison with the usual recommendation (30% – Farar, Young, LaMoreaux, Werth, & Poole, 2001). Since this was however the key judgment criterion we preferred to use a higher threshold compatible with previous recommendations (Goldsmith, Boers, Bombardier, & Tugwell, 1993). A higher cut-off most likely decreases sensitivity of the pre-implantation test.

Satisfaction of the patient was recorded after each injection by lumbar puncture and after the continuous infusion test. This was initially a positive test criterion. However in this study, all patients considered positive had a decrease in VAS score of 40% or more. The satisfaction score in each of these patients was also above 40% however this was not used as a decisive criterion for considering a patient a responder and proposing implantation. In daily practice two options are open to the clinician. One is to take into consideration a standardized satisfaction score and/or use a continuous infusion test. In the view of the authors the satisfaction of patients during the short period after a LP test is difficult to objectively asses whatever the means used. In the present study, the satisfaction score used was a strict minimum and physician discretion is not advisable for the decision to implant a pump.

4.2 | Rationale

Neurophysiological rationale for the use of intathecal ziconotide in the specific setting of spinal cord injury central neuropathic pain is debatable.

Lesions in spinal cord injury alter both local nociceptive neurons (first and second order) but also ascending and descending pathways. Neuropathic pain experienced by SCI patients can be either at-level pain or below level pain in the region of hypoesthesia/anaesthesia (i.e. deafferantation) (Bryce, Biering-Sørensen, et al., 2012; Bryce, Ivan, & Dijkers, 2012; Siddall, 2003).

N-Type Calcium channels (the target of ziconotide) are present in the spinal cord in the dorsal horns and are specific to the nociceptive pathways. Located on axonal termination they provide a trigger for synaptic release of neurotransmitters between the first and second order neurons (Bourinet et al., 2014; Simms & Zamponi, 2014).

Pain at the level of injury may be related to scar tissue formation and histological changes at the site of injury. It is possible that ziconotide acts on local mechanism of pain generation since its specific receptors are situated precisely at this level in the normal spinal cord (Bourinet et al., 2014).

Nevertheless, most patients with SCI injury experience pain in a territory that is mostly below the NLI and often completely deafferented (Bryce, Biering-Sørensen, et al. 2012). This type of pain is thought to arise at supra spinal levels given the interruption or at least severe disruption of spinothalamic tracts. This implies that effects of the treatment above the level of spinal cord injury are necessary to impact on this type of pain. In theory, this is possible since lumbar infusion induces diffusion of the drug in the cisterna magna as shown in animal studies (Wang et al., 2000; Yaksh, de Kater, Dean, Best, & Miljanich, 2013).

Patients in this series experienced the two types of pain and ziconotide showed to be efficient on both. Specific mechanistic conclusions are not available using the data from this study however the impact on at-level pain seems to have been more important than the one on below the level of neurologic injury. Similarly impact on paroxysmal pain seems also to be greater than on continuous pain (85% decrease vs. 35% decrease). These differences were in general not statistically significant therefore only a tendency may be retained from the data presented here. Additionally, blockage of the circulation of the CSF was one of the causes of initial failure of the LP tests and in some patients, it was necessary to implant an infusion catheter above the level of the spinal cord injury to obtain efficacy. This suggests that mechanisms of pain generation and action of the drug at the very least at spinal cord levels just above the injury or perhaps even at supraspinal levels.

Spinal cord injury pain has thus specific mechanisms distinguishing it from other forms of chronic pain. Results and conclusions of this study cannot therefore be extrapolated in any way to other pathologies. Ziconotide has approval for many painful syndromes and this study covers only a very limited proportion of patients. Unfortunately, the converse is also true: due to its specific mechanisms treatment recommendations cannot be made concerning central neuropathic pain based on studies for other pathologies. While these facts are limiting they also add a degree of necessity to this study and its follow-ups.

4.3 | Efficacy

Failure to achieve a significant impact on pain related to SCI by ITZ was mainly due to lack of response during the test phase. This occurred in 25% of patients consisting actual failure of the therapy. This failure rate compares well, and is generally better than the ones described for the few alternative treatments available for such patients, such as intrathecal morphine, spinal cord stimulation or lesioning techniques (Anderson & Burchiel, 1999; Moreno-Duarte et al., 2014; Sindou et al., 2001; Thimineur et al., 2004).

One important possible cause of failure of the intrathecal ziconotide test is a disturbance in the flow of CSF. This was an issue in this group of patients in particular in those presenting

with SCI after trauma. In fact, while no specific studies on the matter are known to the authors, it is reasonable to assume that if the molecule does not reach the injured level and/or levels higher up efficacy will be very limited. In this group in several patients with traumatic SCI MRI (pan medullary sagittal T2) showed disturbances to CSF flow. After the initial LP test a continuous infusion test was performed with positive results in some (three out of the nine with a negative LP test tested positive on a CI test). Additionally in one patient the LP test was not performed on account of CSF flow disturbances found on MRI initially and a continuous infusion test was directly performed (patient 16). On the other hand in two other patients with syringomyelia pretest MRI not having revealed CSF flow disturbances LP tests were considered possible.

The role of pretest MRI is undoubtable from the author's point of view however when CSF flow disturbances are present and LP tests negative only one third of patients tested positive in the CI test. Continuous infusion tests are useful in patients with disturbances of CSF flow if the catheter is placed above the blockage site. They may also be useful in patients whose LP tests are borderline and in those prone to post LP cephalalgia or puncture is foreseeably difficult.

Few studies have addressed the problem of long term stability of ziconotide treatment. In fact to our knowledge at over 3 years average follow-up this is the longest follow-up yet published (Brookes, Eldabe, & Batterham, 2017; Deer et al., 2018). The results show stability of the effect in the long-run albeit with an increase in dose. In fact in those patients in whom the test was positive the dose of ziconotide at last follow-up was twice that at the beginning of continuous infusion (5.6 vs. 3). It is yet unknown if doses of ziconotide constantly increase after the beginning of continuous infusion or whether this is related to the use of ziconotide alone. Given the long life expectancy of patients with neuropathic pain due to SCI constant necessity to increase doses may be an issue.

As a follow-up of this study a randomized control trial on the long-term efficacy of ziconotide was planned. The objective is to assess the long-term efficacy of the treatment in patients having already tested positive. The trial named SPIDOL is registered (trials.org CT NCT 03942848) and benefits from financing by the French national clinical research programme as a grant given after an open competition. It is designed as a placebo controlled double-blinded randomized cross over trial. It will include patients having had a positive test of ITZ either by LP or continuous infusion. Enrolment will start in September 2019 and the trial plans to enroll 50 patients with a 1 year follow-up.

4.4 | Safety

In 15% of patients a good response was observed during the test phase but this was accompanied by severe side effects preventing the use of the chronic therapy. Safety of ITZ treatment is an issue that has been addressed by many previous studies and discontinuation of treatment is commonplace due to side effects of the treatment with rates of discontinuation even above the one cited in our study (Haute Authorite de Sante, 2018).

What is notable in the present study is the fact that in the group of patients with long-term treatment of ziconotide there was no discontinuation of the treatment over the follow-up period. Most adverse effects occurred during the test phase. During this period frequent and important increases in dose are used to see whether patients are responders or not.

Too rapid titration of ITZ has already been reported as a major risk factor for side effects, i.e. acute urinary retention and cognitive and neuropsychiatric adverse reactions, particularly confusion. Nevertheless, other severe adverse effects occurred at very low doses of ITZ (i.e. 1 μg bolus). These were mostly increases in CPK levels with subsequent transitory renal failure. This side effect does not appear to be dose dependent but rather patient dependent. This implies that while for some patients discontinuation of treatment may be avoided by slower titrations in others this is unavoidable rendering ITZ unusable for them. Newer recommendation on the use of ITZ (Bäckryd, 2018) are in the sense of slow titration and the low rate of drug related adverse effects (none declared by the patients in the post-implantation period) are probably related to this prudent use of the drug.

Device related complications have been observed in this study however these did not lead to complete discontinuation of the therapy but rather a temporary interruption of the test mainly due to infections complications of the implanted devices. This type of complication has been previously described in patients requiring continuous chronic infusion of intrathecal treatment and are not related to the drug itself (Thimineur et al., 2004).

In conclusion, this study shows efficacy of ITZ in a group from very specific population in whom other therapeutic options are not available. These data are valuable and justifies the development further studies such as a randomized controlled trial before validating the therapy for this patient group.

REFERENCES

Anderson, V. C., & Burchiel, K. J. (1999). A prospective study of long-term intrathecal morphine in the management of chronic nonmalignant pain. *Neurosurgery*, *44*(2), 289–300-301. https://doi.org/10.1097/00006123-199902000-00026

Attal, N., Cruccu, G., Baron, R., Haanpää, M., Hansson, P., Jensen, T. S., … European Federation of Neurological Societies. (2010, September). EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision *European Journal of Neurology*, *17*(9):1113–e88. https://doi.org/10.1111/j.1468-1331.2010.02999.x. Epub 2010 April 9

Bäckryd, E. (2018, August). Do the potential benefits outweigh the risks? An update on the use of ziconotide in clinical practice. *European Journal of Pain*, *22*(7), 1193–1202. https://doi.org/10.1002/ejp.1229. Epub 2018 April 25

Baddack, U., Frahm, S., Antolin-Fontes, B., Grobe, J., Lipp, M., Müller, G., & Ibañez-Tallon, I. (2015). Suppression of peripheral pain by blockade of voltage-gated calcium 2.2 channels in nociceptors induces RANKL and impairs recovery from inflammatory arthritis in a mouse model. *Arthritis & Rheumatology*, *67*, 1657–1667. https://doi.org/10.1002/art.39094

Boldt, I., Eriks-Hoogland, I., Brinkhof, M. W. G., de Bie, R., Joggi, D., & von Elm, E. (2014). Non-pharmacological interventions for chronic pain in people with spinal cord injury. *Cochrane Database of Systematic Reviews*. Rev. CD009177. https://doi.org/10.1002/14651858.CD009177.pub2

Bourinet, E., Altier, C., Hildebrand, M. E., Trang, T., Salter, M. W., & Zamponi, G. W. (2014). Calcium-permeable ion channels in pain signaling. *Physiological Reviews*, *94*, 81–140. https://doi.org/10.1152/physrev.00023.2013

Brookes, M. E., Eldabe, S., & Batterham, A. (2017). Ziconotide monotherapy: A systematic review of randomised controlled trials. *Current Neuropharmacology*, *15*, 217–231. https://doi.org/10.2174/1570159X14666160210142056

Bryce, T. N., Biering-Sørensen, F., Finnerup, N. B., Cardenas, D. D., Defrin, R., Lundeberg, T., … Dijkers, M. (2012). International spinal cord injury pain classification: Part I. Background and description. March 6–7, 2009. *Spinal Cord*, *50*, 413–417. https://doi.org/10.1038/sc.2011.156

Bryce, T. N., Ivan, E., & Dijkers, M. (2012). Proposed international spinal cord injury pain (ISCIP) classification: Preliminary validation data. *Topics in Spinal Cord Injury Rehabilitation*, *18*, 143–145. https://doi.org/10.1310/sci1802-143

Deer, T., Rauck, R. L., Kim, P., Saulino, M. F., Wallace, M., Grigsby, E. J., … McDowell, G. (2018). Effectiveness and safety of intrathecal ziconotide: Interim analysis of the patient registry of intrathecal ziconotide management (PRIZM). *Pain Practice: the Official Journal of World Institute of Pain*, *18*(2), 230–238. https://doi.org/10.1111/papr.12599

Dijkers, M., Bryce, T., & Zanca, J. (2009). Prevalence of chronic pain after traumatic spinal cord injury: A systematic review. *Journal of Rehabilitation Research and Development*, *46*, 13–29. https://doi.org/10.1682/JRRD.2008.04.0053

Dworkin, R. H., Turk, D. C., McDermott, M. P., Peirce-Sandner, S., Burke, L. B., Cowan, P., … Sampaio, C. (2009, December). Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. *Pain*, *146*(3), 238–244. https://doi.org/10.1016/j.pain.2009.08.019

Farrar, J. T., Young, J. P., LaMoreaux, L., Werth, J. L., & Poole, M. R. (2001, November). Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*, *94*(2), 149–158. https://doi.org/10.1016/S0304-3959(01)00349-9

Goldsmith, C. H., Boers, M., Bombardier, C., & Tugwell, P. (1993, March). Criteria for clinically important changes in outcomes: Development, scoring and evaluation of rheumatoid arthritis patient and trial profiles. OMERACT Committee. *The Journal of Rheumatology*, *20*(3), 561–565.

Haute Autorité de santé. (2018). Transparency committee. Opinion CT 5245: Prialt. May 14th 2008. 9 p. Retrieved from https://www.has-sante.fr/portail/upload/docs/application/pdf/2010-06/prialt_ct_5245.pdf

Moreno-Duarte, I., Morse, L. R., Alam, M., Bikson, M., Zafonte, R., & Fregni, F. (2014, January). Targeted therapies using electrical and magnetic neural stimulation for the treatment of chronic pain in spinal cord injury. *NeuroImage*, *15*(85 Pt 3), 1003–1013. https://doi.org/10.1016/j.neuroimage.2013.05.097

Rauck, R. L., Wallace, M. S., Burton, A. W., Kapural, L., & North, J. M. (2009). Intrathecal ziconotide for neuropathic pain: A review. *Pain Practice*, *9*, 327–337. https://doi.org/10.1111/j.1533-2500.2009.00303.x

Rauck, R. L., Wallace, M. S., Leong, M. S., Minehart, M., Webster, L. R., Charapata, S. G., … Ziconotide 301 Study Group. (2006). A randomized, double-blind, placebo-controlled study of intrathecal ziconotide in adults with severe chronic pain. *Journal of Pain and Symptom Management*, *31*, 393–406. https://doi.org/10.1016/j.jpainsymman.2005.10.003

Riley, J. L., Robinson, M. E., Wise, E. A., Campbell, L. C., Kashikar-Zuck, S., & Gremillion, H. A. (1999). Predicting treatment compliance following facial pain evaluation. *The Journal of Craniomandibular Practice*, *17*, 9–15. https://doi.org/10.1080/08869634.1999.11746072

Siddall, P. J., McClelland, J. M., Rutkowski, S. B., & Cousins, M. J. (2003). A longitudinal study of the prevalence and characteristics of pain in the first 5 years following spinal cord injury. *Pain*, *103*, 249–257. https://doi.org/10.1016/S0304-3959(02)00452-9

Simms, B. A., & Zamponi, G. W. (2014). Neuronal voltage-gated calcium channels: Structure, function, and dysfunction. *Neuron*, *82*(1), 24–45. https://doi.org/10.1016/j.neuron.2014.03.016.

Sindou, M. P., Mertens, P., & Wael, M. (2001, May). Microsurgical DREZotomy for pain due to spinal cord and/or cauda equina injuries: Long-term results in a series of 44 patients. *Pain*, *92*(1–2), 159–171. https://doi.org/10.1016/S0304-3959(00)00487-5

Staats, P. S., Yearwood, T., Charapata, S. G., Presley, R. W., Wallace, M. S., Byas-Smith, M., … Ellis, D. (2004). Intrathecal ziconotide in the treatment of refractory pain in patients with cancer or AIDS: A randomized controlled trial. *JAMA*, *291*, 63–70. https://doi.org/10.1001/jama.291.1.63

Thimineur, M. A., Kravitz, E., & Vodapally, M. S. (2004). Intrathecal opioid treatment for chronic non-malignant pain: A 3-year prospective study. *Pain*, *109*(3), 242–249. https://doi.org/10.1016/j.pain.2004.01.003

Treede, R. D., Jensen, T. S., Campbell, J. N., Cruccu, G., Dostrovsky, J. O., Griffin, J. W., … Serra, J. (2008, April 29). Neuropathic pain: Redefinition and a grading system for clinical and research purposes. *Neurology*, *70*(18), 1630–1635. Epub 2007 November 14. https://doi.org/10.1212/01.wnl.0000282763.29778.59

Wallace, M. S., Charapata, S. G., Fisher, R., Byas-Smith, M., Staats, P. S., Mayo, M., … Ziconotide Nonmalignant Pain Study 96-002 Group. (2006). Intrathecal ziconotide in the treatment of chronic nonmalignant pain: A randomized, double-blind, placebo-controlled clinical trial. *Neuromodulation: Technology at the Neural Interface*, *9*(2), 75–86. https://doi.org/10.1111/j.1525-1403.2006.00055.x

Wang, Y. X., Pettus, M., Gao, D., Phillips, C., & Scott Bowersox, S. (2000). Effects of intrathecal administration of ziconotide, a selective neuronal N-type calcium channel blocker, on mechanical allodynia and heat hyperalgesia in a rat model of postoperative pain. *Pain*, *84*, 151–158. https://doi.org/10.1016/S0304-3959(99)00197-9

Yaksh, T. L., de Kater, A., Dean, R., Best, B. M., & Miljanich, G. P. (2013). Pharmacokinetic analysis of Ziconotide (SNX-111), an intrathecal N-type calcium channel blocking analgesic, delivered by bolus and infusion in the Dog. *Neuromodulation*, *15*(6), 508–519. https://doi.org/10.1111/j.1525-1403.2012.00479.x

Zamponi, G. W., Striessnig, J., Koschak, A., & Dolphin, A. C. (2015). The physiology, pathology, and pharmacology of voltage-gated calcium channels and their future therapeutic potential. *Pharmacological Reviews*, *67*, 821–870. https://doi.org/10.1124/pr.114.009654

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