Retrospective Cohort Study

Italian Registry on Long-Term Intrathecal Ziconotide Treatment

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Background: Ziconotide is commonly used for intrathecal (IT) therapy of chronic pain, and has been recently indicated as a first-line IT drug. It is also extremely useful for patients intolerant or refractory to the common IT drugs (such as morphine). The literature, excluding registration studies, mostly includes small samples, and gives only fragmentary evidence on the long-term risks and benefits of ziconotide.

Objective: To collect data on safety and efficacy of long-term ziconotide IT infusion in Italian pain centers.

Study Design: Retrospective cohort study on the use of ziconotide in Italy. The study was designed and coordinated by the Foundation ISAL (Algological Sciences Research and Training Institute). Patients treated with ziconotide from several pain therapy and neurosurgery units were included in the study, allowing the creation of the first Italian Registry of Ziconotide.

Setting: Seventeen Italian public and private pain and neurosurgery centers.

Methods: Patients suffering from cancer or non-cancer intractable chronic pain who had been treated with ziconotide IT infusion for at least one month. Efficacy was analyzed considering changes on the visual analog scale of pain intensity from baseline observation. Safety was assessed by monitoring the number and intensity of adverse events.

Results: Currently, 104 patients are included in the Italian Registry of Ziconotide. Ziconotide was administered as the first IT drug choice to 55 patients. Seventy-two patients reported at least a 30% pain intensity reduction with a mean dose of 4.36 µg/d. The sustained analgesic effect ($P < 0.001$) of the ziconotide IT therapy was observed in a group of 45 patients who remained in the study over 6 months without treatment interruptions and with relatively stable doses. Sixty-six patients reported at least one side effect related to ziconotide. However, adverse events have not always been decisive for treatment interruptions.

Limitations: Data were collected retrospectively from different pain centers that used different methods for ziconotide treatment and clinical forms for its data collection; for this reason there is an absence of standardized methodologies and a placebo-controlled group, and some data were missing.

Conclusions: Ziconotide IT therapy is a treatment option commonly used for clinical practice in 17 Italian pain therapy and neurosurgery units. It might give relief to patients with refractory chronic pain, and it seems to have a safe profile. Long-term studies and controlled trials are required.:

Key words: ziconotide; registry; drug safety; intrathecal; refractory chronic pain, opioid, adverse events, long-term treatment

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The need for a holistic pharmacovigilance approach in clinical practice has recently emerged from the international literature (1,2), and, in particular, data collection on long-term drug safety and risk management has gained pivotal importance (2). This concept is in accordance with clinical governance, which was first introduced in the United Kingdom in the 1990s in order to improve the quality of health services and risk management, and to maintain high standards of care (3,4). In this context, drug registries (2) allow data collection on a large number of patients, and their results can be used for future clinical studies and guidelines implementations (5-14). For this reason, they are a good tool for safety and impact assessment of drugs in a population of patients who can be followed over time.

Registries of intrathecal (IT) drugs administration (15), and IT delivery systems for chronic pain management have been developed because IT therapies are now considered particularly useful for chronic pain management (16-23). IT therapy, indeed, allows drug administration directly through the cerebrospinal fluid, at the level of the dorsal horns along the spinal cord, the site of the nociceptive primary afferent. The advantages of this therapy are the reduction of systemic side effects and the use of lower drug dosages. Morphine has been the most-used drug for IT treatment until recently. Chronic opioid use, unfortunately, can induce tolerance (24), and patients require increasing opioid dosages.

Ziconotide (Prialt) was recently introduced as a new option for IT treatment. Ziconotide is approved by the US Food and Drug Administration (FDA) and European Agency for the Evaluation of Medicinal Products (EMEA), and its commercialization has been authorized in the European Union since 2005 (25). In 2007, the Polyanalgesic Consensus Conference indicated ziconotide as a "first-line IT analgesic" (26), thanks to its property and efficacy (27-29).

Ziconotide is a non-opioid analgesic, which is indicated for the management of chronic pain in patients who require an IT therapy, but are intolerant or refractory to other analgesic treatments. Ziconotide is a synthetic analogue of ω-conotoxin MVIIA, a 25 – amino acid peptide that is found in Conus magus venom (30). Ziconotide selectively blocks N-type calcium channels, which are highly concentrated on the surface of the presynaptic terminations along the nociceptive pathways (31), and is the first drug expressively developed for the IT route. The most common ziconotide adverse events are: dizziness, somnolence, confusion, abnormal gait, nausea, and memory impairment (29). These effects can be reduced using a slow titration, starting with a dosage of 1.2 μg/day. Adverse events usually disappear a few days after ziconotide interruption (28,32).

The advantages of ziconotide, compared to opioids, include an absence of dependence (31) and tolerance (24), a reduction of the nociception / orphanin FQ levels in the cerebrospinal fluid (33), and an absence of spinal catheter-tip granulomas induction (32,34). Another advantage of ziconotide is that it does not induce hormonal modifications, such as hypogonadism and hyperprolactinemia, and immunosuppression, as has been shown for opioids (33,35,36). For these reasons young patients and patients under therapy with high morphine dosages without good pain relief—or refractory to other IT therapies—are good candidates for ziconotide treatment.

The manufacturer recommends that ziconotide should be used as IT monotherapy. We designed a protocol (the Raffaeli Detoxification Model) to allow the switch from IT opioids to ziconotide in a short time (37), for those patients who have developed IT opioid tolerance.

The combination of ziconotide and other systemic or IT drugs is well reported (32,38,39). It has been observed, for example, that combined administration of ziconotide and baclofen might be an option to treat neuropathic pain associated with spasticity (40). Administration of ziconotide combined with IT morphine, moreover, might reduce pain intensity and allow lower systemic opioid consumption (38,39).

The current literature on ziconotide, however, includes only a few published studies (other than registration studies) with small samples, reports fragmentary evidence on the long-term risk and benefits of ziconotide (41), and categories of patients with the best indication for this treatment option are not clearly identified (28,42). For these reasons, studies (observational and randomized trials) on the drug's safety and risk management are necessary, especially those involving data collection on a large number of patients, in order to integrate isolated experiences and produce experimental hypothesis (43).

For these reasons, we started an observational retrospective study on long-term ziconotide treatment, involving several Italian pain centers, in order to build the first Italian Ziconotide Registry.

Methods

Participants

The study was approved by the Institutional Review Board (IRB). Patients who were treated with ziconotide from January 2007 to May 2010 were included in the registry if they met the following criteria: 18 years of age or older, suffering from at least 6 months of cancer or non-cancer intractable chronic pain, unsatisfactory responses to other systemic or IT therapies, ziconotide IT infusion treatment for at least one month, external IT catheter or an implanted infusion system for ziconotide IT therapy.

Exclusion criteria: ziconotide hypersensitivity or IT analgesic contraindications; history of psychiatric disorder or pathological dependence; IT catheter de-positioning, as detected by a radiograph before the data collection; pregnancy.

Data collection

Before starting the data collection, a literature review on ziconotide and clinical registries was performed (5-9,15,16) in order to select relevant clinical aspects for the study's Case Report Forms (CRF) and build the registry's database. A preliminary CRF was tested by administering it to a small group of clinicians working at the pain therapy units at the Infermi Hospital (Rimini) and Salvatore Maugeri Foundation IRCCS (Pavia).

The final CRF was then created for the evaluation of medical data, particularly chronic pain treatment by IT infusion systems, and was distributed to 17 pain therapy centers that agreed to participate in the study (Appendix 1).

A CRF (16 items), containing clinical information related to ziconotide administration and characteristics of drug infusion systems, was used for the data collection. The form, in particular, included the following data: demographic data; medical history; pain classification; analgesic therapies used before ziconotide; ziconotide dosages and concomitant therapies; pain intensity (at baseline and at each phase of ziconotide administration); type of IT infusion system (external IT catheter/ implanted infusion system); adverse events and related probable causes; treatment interruption and related causes.

Pain intensity was assessed using the visual analogue scale (VAS; 11-point scale, 0 representing no pain and 10 representing the worst pain imaginable). Pain characteristics were classified using International Association for the Study of Pain (IASP) references (44). Efficacy was assessed by analyzing changes on the VAS of pain intensity from baseline observation. Ziconotide safety was assessed by monitoring the number and intensity of adverse events. Adverse events were categorized according to MedDRA (Medical Dictionary for Regulatory Activities, MSSO).

Statistical Analysis

A descriptive statistical analysis was used. Continuous data of the whole sample were reported as the mean and ± standard deviation, and were analyzed with the t-test, and Kruskall-Wallis test for small number groups using SAS version 9.2 (SAS Inc., Cary, NC) software. Statistical significance was defined as $P< 0.05$. Proportions are expressed in percentage.

Results

Study Population

The Italian Registry of Ziconotide comprises 104 patients. Their demographic and baseline characteristics are shown in Table 1. The majority of patients suffered from non-cancer pain (69%) with different etiologies. Ziconotide was administered as the first IT drug to 55 (52.88%) patients (35 with non-cancer pain, 20 with cancer pain), whereas 49 (47.11%) patients (37 with non-cancer pain, 12 with cancer pain) had been previously treated with IT morphine. Thirty-eight (36.53%) patients (12 cancer, 26 non-cancer) started their ziconotide infusion via an external IT catheter and 61 patients (58.65%) (20 cancer, 41 non-cancer) used a totally implanted infusion system; for 5 non-cancer patients the infusion system was not indicated.

The main reasons for ziconotide therapy use were the following: severe chronic pain refractory to other therapies for 76 patients (73.07%, 20 cancer, 56 non-cancer), and intolerance to previous treatments for 10 patients (9.61%, 3 cancer, 7 non-cancer). Mean initial ziconotide dose (n=104) was 1.41 ± 0.61 μg/d, in particular, the dosage was 1.81 ± 0.68 μg/d and 1.24 ± 0.48 μg/d for patients with cancer pain and non-cancer pain respectively.

Efficacy and drug dosing

Mean baseline VAS (n=101) was 8.56 ± 1.55; in particular, VAS value was 8.90 ± 1.78, and 8.41 ± 1.42 for patients with cancer pain and non-cancer pain respectively. Pain intensity reduction was attained after one month of ziconotide treatment (Fig. 1). Seventy-two patients (69.23%) reported at least a 30% pain inten-

Table 1. *Demographic and baseline characteristics*

	Total	Cancer pain	Non-cancer pain
Patients N	104	32	72
Sex - N (%)			
Male	43 (41.34)	16 (50)	27 (37.50)
Female	61 (58.65)	16 (50)	45 (62.50)
Age			
Mean	63.76	66	63
SD	11.62	9.37	12.20
Median (range)	66.2 (29.8 – 83.3)	64.8 (49 – 83.3)	66.8 (29.8 – 83.3)
Race - N (%)			
Caucasian	95 (91.34)	27 (84.37)	68 (94.44)
Not collected	9 (8.65)	5 (15.62)	4 (5.55)
Medical diagnosis - N (%)			
FBSS	26 (25)	0	26 (36.11)
CBLP	13 (12.50)	0	13 (18.05)
Myelopathy / Central Pain Syndrome	16 (15.38)	0	16 (22.22)
Polyneuropathy, PNL, Post-Herpes	15 (14.42)	0	15 (20.83)
Cancer	32 (30.76)	32 (100)	0
Arthrosis	2 (1.92)	0	2 (2.77)
Pain classification - N (%)			
Neuropathic	53 (50.96%)	1	52 (72.22)
Nociceptive	7 (6.73)	3 (9.37)	4 (5.55)
Mixed	27 (25.96)	13 (40.62)	14 (19.44)
Not collected / Not applicable	17 (16.34)	15 (46.87)	2 (2.77)
Diagnosis of cancer - N (%)			
Breast	2 (1.92)	2 (6.25)	0
Lungs	8 (7.69)	8 (25)	0
Colorectal	4 (3.84)	4 (12.50)	0
Other	10 (9.61)	10 (31.25)	0
Not collected	3 (2.88)	1 (3.12)	0
Not applicable	77 (74.03)	7 (21.87)	0
Metastasis - N (%)			
No	87 (83.65)	15 (46.87)	72 (100)
Yes	17 (16.34)	17 (53.12)	0

Abbreviations: FBSS, Failed Backs Surgery Syndrome; CBLP, Chronic Back and Leg Pain; PNL, Peripheral Nerve Lesions

sity reduction (Fig. 2) with a mean dose of 4.36 µg/d (Table 2), within a mean treatment period of 53 days (n=68). Fifty-six patients (53.84%) experienced a 50% pain intensity reduction and 52 of those experienced this reduction within a mean treatment period of 82 days. Cancer patients attained 20%-50% pain reduction within one month of treatment on average (range: 29-37 days). Non-cancer patients attained a 20%-50% pain reduction within 3 months of treatment on average (range: 62-112). Drug dosages are reported in Table 2.

A further analysis was made on 45 patients (24 naïve for IT therapy and 21 non-naïve) who remained in the study for more than 6 months without treatment interruptions. In this group, 31 were treated with ziconotide as the only IT drug, whereas 14 were treated with ziconotide in combination with morphine, anes-

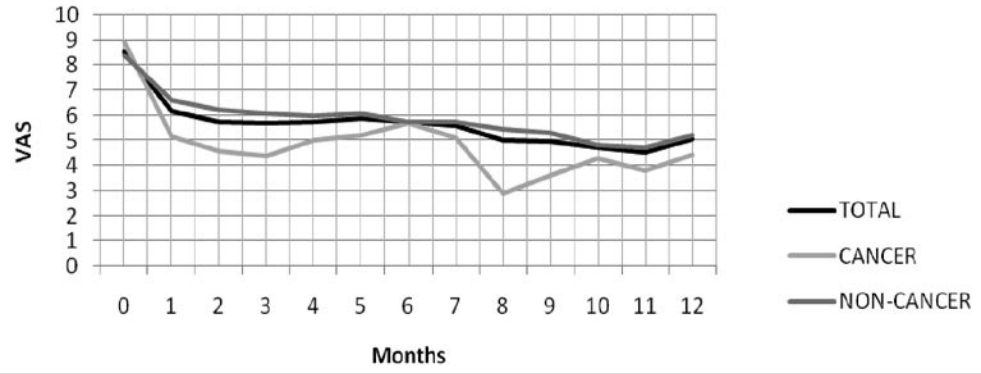

Fig. 1. *VAS scores over 12 Months*

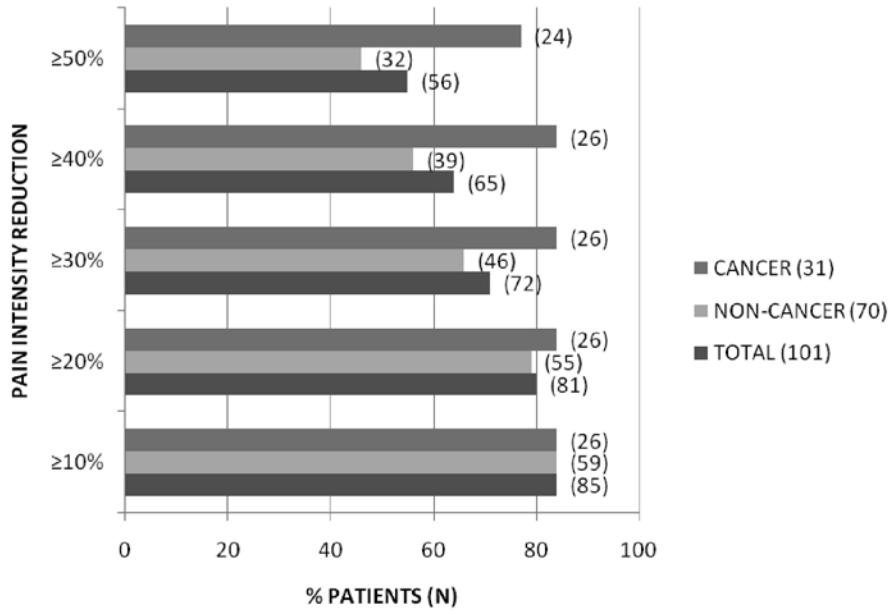

Fig. 2. *Pain Intensity reduction*

Table 2. *Pain Intensity reduction and Doses*

Dose (µg/day)	≥10%	≥20%	≥30%	≥40%	≥50%
Cancer					
Mean (Std)	4.13 (2.13)	4.73 (2.37)	5.10 (2.45)	5.54 (2.3)	5.5 (2.21)
Median (range)	3.8 (1.2 – 9.6)	4.4 (2 – 9.6)	4.8 (2 – 9.6)	5.2 (2 – 9.6)	4.8 (2 – 9.6)
Non-cancer					
Mean (Std)	3.23 (2.61)	3.65 (2.76)	3.95 (2.93)	4.34 (3.22)	4.59 (3.38)
Median (range)	2.4 (0.5 – 11.2)	2.5 (0.5 – 11.2)	2.8 (0.5 – 11.2)	3 (0.5 – 11.2)	3.2 (0.5 – 11.2)
Total					
Mean (Std)	3.50 (2.50)	3.99 (2.68)	4.36 (2.8)	4.85 (2.93)	4.98 (2.95)
Median (range)	2.4 (0.5 – 11.2)	3 (05 – 11.2)	3.6 (0.5 – 11.2)	4.4 (0.5 – 11.2)	4.8 (0.5 – 11.2)

thetics (bupivacaine) or baclofen. These other drugs were not previously sufficient to provide acceptable pain relief. Constant and significant analgesic effect (P<0.01) of the treatment with ziconotide was observed through 6 months (Fig. 3). Ziconotide dosages at the different time points are reported in Table 3. In the selected group, mean dose at the 6-month evaluation was 4.5 µg/d (SD 2.5).

Safety

No serious adverse event was observed as a consequence of ziconotide treatment. Sixty-six patients (63.46%) reported at least one ziconotide-related side effect. The most common ziconotide-related adverse events were: psychomotor disorders (34.61% of patients) manifested as confusion and memory impairment, and asthenia (22.11% of patients). Other ziconotide-related adverse events are summarized in Table 4. Side effects did not always lead to the decision to discontinue ziconotide therapy, and 45 patients continued the treatment over 6 months.

The main reasons for ziconotide treatment interruption were: 18.26% adverse events (19 non-cancer patients), 6.73% uncontrolled pain (6 non-cancer, 1 cancer),

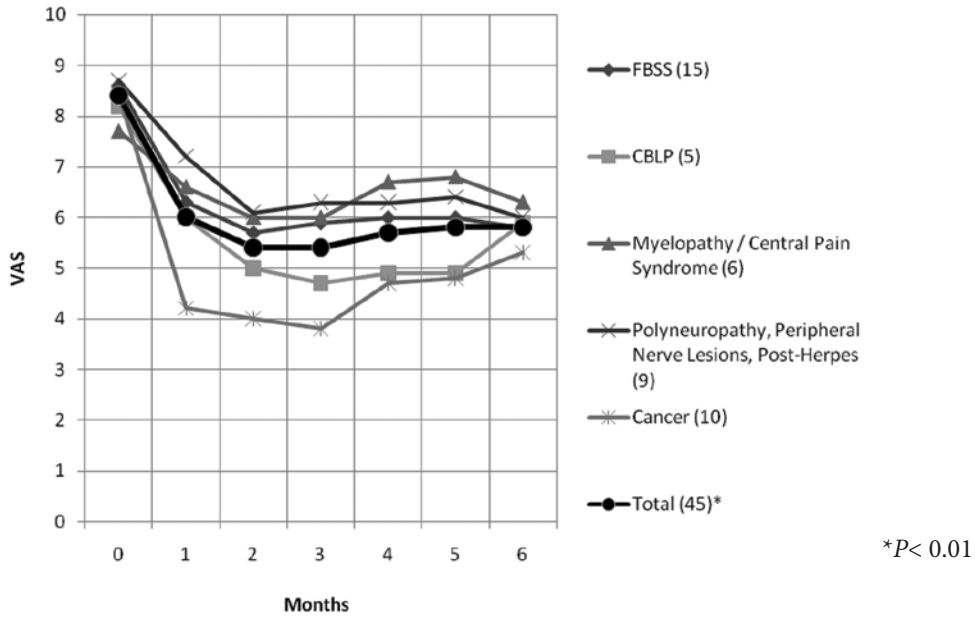

Fig. 3. *VAS scores among 45 patients remaining in treatment over 6 months. There was a significant (p<0.01) reduction in VAS score already after one month of treatment, which was maintained constant up to six months. No significant differences were observed in VAS reduction among the different diagnosis.*

Table 3. *Mean (SD) µg/day Ziconotide doses in 45 patients remaining in treatment over 6 months*

	Months						
	0	1	2	3	4	5	6
FBSS	1.3 (0.6)	4.5 (3.3)	5.2 (3.1)	5.3 (3.1)	5.2 (3.2)	5.1 (3.4)	5.1 (3.5)
CBLP	1.1 (0.1)	1.9 (1.1)	3 (1.9)	3.5 (2.1)	3.7 (1.8)	3.7 (1.8)	4.3 (1.9)
Myelopathy / Central Pain Syndrome	1.4 (0.5)	3.3 (2.3)	2.9 (1.7)	3.3 (1.9)	3.4 (1.7)	3.1 (1.6)	4.2 (1.4)
Polyneuropathy, PNL, Post-Herpes	1.2 (0.6)	2.2 (0.9)	3.4 (1.9)	3.3 (1.9)	3.5 (2)	3.1 (1.3)	3.2 (1.3)
Cancer	1.8 (0.6)	3.7 (1.7)	4.5 (1.7)	4.7 (1.9)	4.3 (1.9)	4.5 (1.8)	4.9 (2.3)
Total	1.4 (0.6)	3.4 (2.4)	4.1 (2.4)	4.3 (2.4)	4.3 (2.4)	4.2 (2.4)	4.5 (2.5)

5.76% lack of compliance (5 non-cancer, 1 cancer), 3.84% infusion system-related adverse events (4 non-cancer). 18 cancer patients and 1 non-cancer patient died during the treatment period because of their disease.

Discussion

In 2007, the Polyanalgesic Consensus Conference indicated ziconotide as a "first-line intrathecal analgesic" (26), and in the same year ziconotide was first introduced in Italy. Since then physicians have used it for different pathologies and in combination with other drugs. We performed a retrospective study of 17 pain therapy units in Italy to create the first Italian Registry of Ziconotide, in order to collect and share information about ziconotide utilization in clinical practice. We were particularly interested in monitoring ziconotide long- term safety, and clarify ziconotide indication.

Our data on ziconotide efficacy and safety were comparable with those reported in other studies; none were placebo-controlled clinical trials (38,39,45). Sixty-seven percent of patients reported a 30% mean reduction in pain intensity after 2 months of treatment; and 55% reported a 50% pain intensity reduction after 3 months of therapy. These results were confirmed by other studies (37,45). In the subset of patients (43%) that continued the ziconotide treatment for more than 6 months, moreover, the mean VAS reduction after 12 months of ziconotide treatment was comparable to that found by Ellis and colleagues (45), showing a 36.9% pain reduction in a sample with characteristics similar to our study population. We were able to attain better pain reduction results than those of Wallace and colleagues, who reported a 31.2% pain reduction (28). We also reported a higher percentage of patients responding to ziconotide treatment (43% versus 33.7%). This might be due to the type of sample used; indeed, Wallace and colleagues (28) selected only patients refractory or intolerant to opioids suffering with non cancer pain, which was the first ziconotide indication (25). Our sample, on the contrary, contained both cancer and non-cancer pain patients, patients naïve to IT therapies, and was used as a first choice in 53% of the patients.

This suggests that ziconotide can be an advantage compared to classic IT therapies (morphine, local anaestics, and baclofen), since the majority of therapies used with patients (73%) before ziconotide administration had not determined a satisfactory pain reduction, or those therapies were interrupted for their related side effects (10%). The mean initial ziconotide dose was 1.41 µg/d, in agreement with studies suggesting low doses at the start of infusion (1.2 µg/d) and slow titration (40). A ziconotide dosage increase was prescribed in the first 2 months; it did not change significantly up to 6 months of treatment. Mean ziconotide dosages were 4.36 ± 2.4 µg/d at 3 months and 4.5 ± 2.5 µg/d at 6 months, which are lower than those reported by Ellis and colleagues (45) and similar to those reported by Wallace et al (38).

We observed the most common ziconotide-related side effects as previously reported in the literature: altered mood, confusion, memory deficit, abnormal CPK levels, vertigo, nausea (28,38,39,45). They were mostly of mild or moderate intensity, however, no serious adverse events were observed and they did not always cause treatment interruption (18%). This result is comparable to those of other studies (38,39,45). Ellis and colleagues (45), in particular, showed similar side effects prevalence (confusion 43%, dizziness 32%, memory impairment 25%, CPK increase 7%, and nausea 14%); they were reversible with dose reduction or discontinuation. These findings are similar to our results, indeed, we observed that after treatment discontinuation, adverse events reversed within a few days. The subsequent resumption of ziconotide therapy at lower dosages,

Table 4. *Adverse events related to Ziconotide*

Adverse Events	No of patients	%
Psychomotor disorders	36	34,61
Asthenia	23	22,11
Balance disorders	21	20,19
Sensory impairments	16	15,38
Altered muscle tone	15	14,42
Motor coordination disorders	13	12,5
Neurovegetative disorders	10	9,61
Nausea / Appetite absent	10	9,61
Oral cavity disorders	8	7,69
Hallucinations	8	7,69
Psychiatric disorders	6	5,76
Gastroenteric disorders	6	5,76
Sleeplessness	5	4,8
CPK abnormal	5	4,8
Dysuria	4	3,84
Altered Mood	4	3,84
Aggressiveness	4	3,84
Headache	4	3,84
Hypotension	3	2,88
Tinnitus	2	1,92
Hypertension	2	1,92

moreover, allowed achieving an analgesic effect while reducing adverse events. The group who remained in treatment for more than 6 months showed constant pain relief at stable doses of ziconotide, and there were no serious adverse events that caused therapy interruption. This suggests that, once the early side effects were overcome, the patients were not exposed to long-term risks. The constant ziconotide dosages also suggest the absence of tolerance effect.

Concerning the indication for ziconotide treatment, we performed an efficacy analysis among different classes of pathologies, however no significant differences in the long-term efficacy of ziconotide therapy and drug dosages were observed, as well as between naïve or non-naïve to IT therapy patients. We note the interesting observation of the choice of ziconotide as the first-line IT drug for 53% of patients, in accordance with the Polyanalgesic Consensus Conference indications of 2007 (16), and as proof of the need to find alternative treatments to morphine.

This high percentage was in part due to the composition of the present study's sample; indeed, 51% of patients suffered from neuropathic pain (myelopathy / central pain syndrome 15.38%, and polyneuropathy, post-herpes 14.42%), which is one of the main indications for ziconotide therapy as reported in the literature. This proportion of neuropathic pain and the need of some physicians to find alternative treatments to morphine in order to avoid tolerance, and opioid-induced adverse events, explained the high percentage of ziconotide as the first drug choice. Most Italian centers, moreover, use a selection test before proceeding with the implantation of a permanent IT drug infusion system. This trial is performed to assess efficacy and tolerability of intraspinal analgesia infusion, and choose the drug for the IT infusion, as described in our previous work (16). Ziconotide was also used as the first choice for those patients non-responsive to the test or refractory or intolerant to systemic opioids.

This survey has limitations common to observational studies, such as the absence of standardized methodologies and a placebo-controlled study group. It has permitted, nonetheless, sharing the clinical experience of different physicians. Another limitation might be due to the difficulty of data collection, since the study was retrospective and the physicians involved did not use the same clinical report form (CRF); hence, some data were missing. For this reason we are planning to implement the register with a prospective study, using a common CRF for each center, monitoring long term efficacy (pain, disability and quality of life), and safety, including a neuro-hormonal profile, the risk of tolerance occurrence, and the impact on the nociceptive system.

In the subset of patients (43%) that continued the ziconotide treatment for more than 6 months, 14 patients (13.46%) were treated with ziconotide in combination with morphine, anesthetics (bupivacaine) or baclofen, because these other drugs were not previously sufficient to determine an acceptable pain relief. We know that the ziconotide mixtures with other drugs, in particular with morphine, reduce its stability and half-life. For this reason we developed the Raffaeli detoxification model (37) for the rapid detoxification from IT morphine, allowing the start of ziconotide treatment within 2 weeks. The use of ziconotide in combination with morphine has been previously reported (38,39). For this reason, some Italian physicians preferred the slow detoxification, decreasing morphine and adding increasing dosages of ziconotide, until the attainment of a stable morphine/ziconotide ratio that guaranteed a satisfactory pain relief for patients. The refill was performed at variable ranges of time, according to the physician's experience; nonetheless, none of them signaled a change in refill modality because of morphine/ziconotide mixtures.

The biochemical stability issue of morphine/ziconotide mixtures should not be underestimated. For this reason we believe that studies regarding the stability of IT drugs mixtures are of pivotal importance to improve patients' safety.

Conclusion

Ziconotide can be used as a first choice for intrathecal pain treatment or in substitution to classic IT drugs (morphine), with good levels of efficacy and long-term safety. Ziconotide did not cause severe side effects. Long-term treatment was attained at stable doses with constant pain relief, without long-term adverse events that caused therapy interruption. This suggests that, once the early side effects were overcome, the responsive patients were not exposed to long-term risks. The constant ziconotide dosages also suggest the absence of tolerance effect.

Appendix 1. *Italian Physicians participating in the study*

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- Dario A. MD, Circolo Foundation Macchi Hospital, Varese
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- De Rose M. MD, "Germaneto" University Policlinic, Catanzaro
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- Lippolis S. MD, Edoardo Agnelli Civil Hospital, Pinerolo
- Mameli S. MD, Businco, Hospital, Cagliari
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- Poli P. MD, Santa Chiara Hospital, Pisa
- Raffaeli W. MD, Infermi Hospital, Rimini
- Reverberi C. MD, Oglio Po', Hospital Vicomoscano / Casalmaggiore
- Ricci V. MD, Lugo Hospital, Ravenna
- Rocco M. MD, Regina Margherita Hospital, Castelfranco Emilia
- Russo R. MD, Azienda ospedaliera "Pugliese – Ciaccio", Catanzaro

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