SHORT COMMUNICATION

Direct conversion from tramadol to tapentadol prolonged release for moderate to severe, chronic malignant tumour-related pain

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Abstract

Background: A recent randomized-withdrawal, active- and placebo-controlled, double-blind phase 3 study showed that tapentadol prolonged release (PR) was effective and well tolerated for managing moderate to severe, chronic malignant tumour-related pain in patients who were opioid naive or dissatisfied with current treatment (*Pain Physician*, 2014, 17, 329–343). This post hoc, subgroup analysis evaluated the efficacy and tolerability of tapentadol PR in patients who previously received and were dissatisfied with tramadol for any reason and who had a pain intensity ≥5 (11-point numerical rating scale) before converting directly to tapentadol PR.

Methods: In the original study, eligible patients had been randomized (2:1) and titrated to their optimal dose of tapentadol PR (100–250 mg bid) or morphine sulphate-controlled release (40–100 mg bid) over 2 weeks. The present report focuses on results during the titration period for a subgroup of patients randomized to tapentadol PR after having been on tramadol treatment prior to randomization in the study ($n = 129$). Results for this subgroup are compared with results for all 338 patients who received tapentadol PR during titration (overall tapentadol PR group).

Results: Responder rates (responders: completed titration, mean pain intensity <5 [0–10 scale] and ≤20 mg/day rescue medication during last 3 days) were slightly better for the tramadol/tapentadol PR subgroup (69.8% [90/129]) vs. the overall tapentadol PR group (63.9% [214/335]). Tolerability profiles were comparable for both groups.

Conclusions: Results of this subgroup analysis indicate that patients with cancer pain could safely switch from prior treatment with the weak centrally acting analgesic tramadol directly to the strong centrally acting analgesic tapentadol PR, for an improved analgesic therapy for severe pain.

What does this study add?
- Results of this post hoc analysis show that patients who had received prior tramadol therapy could switch directly to tapentadol PR, with the majority (~70%) experiencing improved efficacy.

1. Introduction

World Health Organization (WHO) step 2 analgesics, including the weak centrally acting analgesic tramadol, are often used for the management of moderate or moderate to severe, chronic cancer-related pain (Leppert and Luczak, 2005; Vargas-Schaffer, 2010). Tramadol, which has a favourable tolerability

profile compared with strong classical opioid analgesics, is often initially preferred for patients with moderate to severe cancer-related pain (Leppert and Luczak, 2005). When pain worsens, patients may need to be switched to a WHO step 3 analgesic (Vargas-Schaffer, 2010). Strong classical opioid (WHO step 3) analgesics, such as morphine, may be associated with poor tolerability (Droney and Riley, 2009). Tapentadol prolonged release (PR), a centrally acting WHO step 3 analgesic with two mechanisms of action [μ-opioid receptor agonism and noradrenaline reuptake inhibition (Tzschentke et al., 2006, 2009; Kress, 2010)], has been shown to be effective and well tolerated for the management of moderate to severe, chronic malignant tumour-related pain (Imanaka et al., 2013, 2014; Kress et al., 2014), with improved gastrointestinal tolerability compared with morphine controlled release (CR) (Kress et al., 2014) and oxycodone CR (Imanaka et al., 2013). Results of a recent, randomized-withdrawal, parallel-group, active- and placebo-controlled, double-blind phase 3 study (Kress et al., 2014) (ClinicalTrials.gov Identifier: NCT00472303) showed that tapentadol PR (100–250 mg bid) was effective for the management of moderate to severe, chronic cancer pain with non-inferior analgesic efficacy to that of morphine CR (40–100 mg bid). Because of the randomized-withdrawal design of the maintenance period for that study, the non-inferiority comparison was limited to the 2-week titration period (a potential limitation of the results) (Kress et al., 2014). In that study, tapentadol PR was associated with lower incidences of overall side effects and gastrointestinal side effects than morphine CR during the titration period (Kress et al., 2014). The current analysis of data from that phase 3 study evaluated the efficacy and tolerability of tapentadol PR in a subgroup of patients who had previously received tramadol and had converted directly to tapentadol PR treatment for the 2-week titration period.

2. Methods

2.1 Patients and study design

The multicentre, controlled, double-blind phase 3 study (NCT00472303) included a screening period lasting up to 7 days, a 2-week titration period and a 4-week maintenance period. Details of the patient selection, study design and analyses for the full study population have been published previously (Kress et al., 2014). Briefly summarized, the study included adult patients with moderate to severe, chronic, malignant tumour-related pain [pain intensity ≥5 on an 11-point numerical rating scale (NRS) under their prior analgesic regimen at the start of titration, including tramadol or other opioids], who were opioid naive or dissatisfied with their current analgesic treatment (doses of tramadol or other opioids equivalent to oral morphine ≤160 mg/day).

The study included an initial screening period of up to 7 days duration, during which patients could continue taking their previous analgesic (e.g. tramadol) treatment. Starting on the day of randomization, which immediately followed the screening period, patients were not permitted to take any analgesics other than the study drug (tapentadol PR or morphine CR) and morphine immediate release (IR) tablets as rescue medication as needed. Eligible patients were randomized (2:1) and titrated in a double-blind manner to their optimal dose of tapentadol PR (100–250 mg bid) or morphine sulphate CR (40–100 mg bid) over 2 weeks. During stepwise titration, oral morphine sulphate IR 10 mg was permitted as rescue medication as needed (no maximum dose). Patients in the tapentadol PR titration group who met the prespecified response criteria that were published previously (Kress et al., 2014) (and are described below under *Study evaluations and statistical analyses*) were re-randomized to tapentadol PR or placebo bid in a double-blind manner for a 4-week maintenance period. Patients in the morphine CR titration group continued to receive morphine CR during the 4-week maintenance period; these patients were not included in the present post hoc analysis. Thus, the present report will focus only on results for patients randomized to tapentadol PR after having been on tramadol treatment prior to randomization in the study.

2.2 Study evaluations and statistical analyses

Only data collected during the tapentadol PR titration period (immediately after switching from tramadol to tapentadol PR) were evaluated for this subgroup of patients pretreated with any formulation of tramadol. Current pain intensity and average daily pain intensity at baseline of the titration period, Week 1, and Week 2, along with changes from baseline, were analysed. Pain intensity was evaluated using observed-case analysis and the last observation carried forward (LOCF), baseline observation carried forward (BOCF) and worst observation carried forward (WOCF) for imputing missing values. Responder rates were also evaluated for the titration period. A responder was defined as a patient who completed

the titration period, had a mean pain intensity score <5 (11-point NRS; patient self-recorded twice daily) during the last 3 days of titration and had a mean dose of consumption of rescue medication ≤20 mg/day during the last 3 days of titration. Treatment exposure and rescue medication use are summarized using descriptive statistics and frequency counts. Incidences of treatment-emergent adverse events (TEAEs) were measured using frequency counts. The full analysis population for the titration period (all patients who received ≥1 dose of study drug during the titration period) was used for all analyses. Results for this subgroup of patients who had received prior tramadol treatment were compared with those of the overall population of patients receiving tapentadol PR. No formal statistical analyses were performed to compare the data for the subgroup who had received prior tramadol treatment and the data for the overall population of patients receiving tapentadol PR. Formal statistical testing between the overall population of patients receiving tapentadol PR and the subgroup was not considered statistically valid because these were not independent populations of patients (i.e. the subgroup of patients receiving tramadol prior to tapentadol treatment was also included in the overall population), and also because this subgroup analysis was not powered or prespecified for comparison to the main population in this study.

3. Results

3.1 Patients and treatment exposure

Overall, 338 patients were randomized to and received treatment with tapentadol PR during the titration period (overall tapentadol PR group), whereas a subgroup of 129 of those patients had received prior therapy with tramadol within 3 days before randomization to tapentadol PR (tramadol/tapentadol PR subgroup). Demographic and baseline characteristics were comparable for patients in the tramadol/tapentadol PR subgroup and the overall tapentadol PR group (Table 1).

Tramadol was the most frequently used centrally acting analgesic prior to initiating study treatment with tapentadol PR; 46.2% (156/338) of patients in the tapentadol PR group had taken tramadol at any time during the 30 days prior to the start of the study. The most common classical opioid analgesics taken during the 30 days prior to starting tapentadol PR treatment by ≥5% of patients were morphine [19.5% (66/338)], fentanyl [20.4% (69/338)], oxy-

codone [7.4% (25/338)], hydromorphone [6.2% (21/338)] and dihydrocodeine [5.6% (19/338)]. Patients may have been taking ≥1 opioid concomitantly prior to entering the study.

The percentage of patients who discontinued treatment during the titration period was comparable in the tramadol/tapentadol PR subgroup and the overall tapentadol PR group, as were the reasons for discontinuation (Table 2). The mean daily dose and mean modal dose of tapentadol PR during the titration period were similar in the tramadol/tapentadol PR subgroup and overall tapentadol PR group (Table 3). The mean duration of exposure to tapentadol PR was approximately 13 days in both the tramadol/ tapentadol PR subgroup and the overall tapentadol PR group (Table 3).

3.2 Efficacy

During the titration period (Supporting Information Table S1), the mean [standard deviation (SD)] decreases in average current pain intensity from baseline to Week 1 and from baseline to Week 2 of titration (LOCF) were comparable in the tramadol/ tapentadol PR subgroup [mean (SD) change: baseline

Table 1 Demographic and baseline characteristics (full analysis population titration for tramadol/tapentadol PR subgroup; safety population titration for overall tapentadol PR group).[a]

	Tramadol/ tapentadol PR subgroup (n = 129)	Overall tapentadol PR group (n = 338)
Mean (SD) age	60.9 (10.73)	59.8 (10.39)
Age category, n (%)		
<65 years	79 (61.2)	224 (66.3)
≥65 years	50 (38.8)	114 (33.7)
Gender, n (%)		
Male	70 (54.3)	188 (55.6)
Female	59 (45.7)	150 (44.4)
Race, n (%)		
White	129 (100)	338 (100)
Mean (SD) BMI, kg/m^2	24.6 (5.12)	25.0 (5.27)
Neuropathic pain present, n (%)	84 (65.1)	222 (65.7)
Visceral pain present, n (%)	65 (50.4)	166 (49.1)
Nociceptive pain present, n (%)	85 (65.9)	236 (69.8)
Prior opioid treatment received, n (%)	129 (100)	298 (88.2)
Mean (SD) baseline pain intensity[b]	6.4 (1.31)	6.4 (1.46)

PR, prolonged release; SD, standard deviation; BMI, body mass index; NRS, numerical rating scale.

[a]For the tramadol/tapentadol PR subgroup, the full analysis population for the titration period is the same as the safety population for the titration period.

[b]Pain intensity was rated on an 11-point NRS (0 = "no pain" to 10 = "pain as bad as you can imagine").

Table 2 Reasons for treatment discontinuation during the titration period (full analysis population titration for tramadol/tapentadol PR subgroup; safety population titration for overall tapentadol PR group).[a]

Reason for discontinuation, n (%)	Tramadol/ tapentadol PR subgroup (n = 129)	Overall tapentadol PR group (n = 338)
Discontinued for any reason	20 (15.5)	59 (17.5)
Adverse events	5 (3.9)	22 (6.5)
Patient choice (withdrawal of consent)	8 (6.2)	16 (4.7)
Death	2 (1.6)	4 (1.2)
Lack of efficacy	2 (1.6)	10 (3.0)
Study drug non-compliant	1 (0.8)	4 (1.2)
Other	2 (1.6)	3 (0.9)

PR, prolonged release.

[a]For the tramadol/tapentadol PR subgroup, the full analysis population for the titration period was the same as the safety population for the titration period.

Table 3 Dose and duration of exposure to tapentadol PR (full analysis population titration for tramadol/tapentadol PR subgroup; safety population titration for overall tapentadol PR group).[a,b]

	Tramadol/ tapentadol PR subgroup (n = 129)	Overall tapentadol PR group (n = 338)
Mean daily dose, mg		
Mean (SD)	264.5 (63.58)	276.1 (66.66)
Median (range)	264.3 (150, 382)	278.6 (100, 386)
Modal dose,[c] mg		
Mean (SD)	284.5 (101.13)	302.7 (107.56)
Median (range)	300 (100, 500)	300 (100, 500)
Total duration, days		
Mean (SD)	13.2 (2.90)	13.0 (3.09)
Median (range)	14 (2, 18)	14 (2, 18)
Category, n (%)		
≤7 days	10 (7.8)	32 (9.5)
8–14 days	92 (71.3)	235 (69.5)
≥15 days	27 (20.9)	71 (21.0)

PR, prolonged release; SD, standard deviation.

[a]For the tramadol/tapentadol PR subgroup, the full analysis population for the titration period is the same as the safety population for the titration period.

[b]Data shown are only for the titration period.

[c]Tramadol/tapentadol PR subgroup, n = 129; overall tapentadol PR group, n = 337.

to Week 1, −1.4 (1.56); baseline to Week 2, −2.4 (2.01)] and the overall tapentadol PR group [−1.0 (1.58) and −2.1 (2.05), respectively]. Mean (SD) decreases in average daily pain intensity during the titration period (LOCF) were also comparable in the

tramadol/tapentadol PR subgroup [mean (SD) change: baseline to Week 1, −1.3 (1.50); baseline to Week 2, −2.1 (1.90)] and the overall tapentadol PR group [−1.0 (1.51) and −2.0 (1.95), respectively]. Similar decreases in average current pain intensity and average daily pain intensity during the titration period were observed in each of the treatment groups with observed-case analysis, BOCF and WOCF, and these decreases were generally comparable in the tramadol/tapentadol PR subgroup and the overall tapentadol PR group (Supporting Information Table S1).

Response rates during the titration period were high and similar in both the tramadol/tapentadol PR subgroup [69.8% (90/129)] and in the overall tapentadol PR group [63.9% (214/335)]. The most common reason for non-response during the titration period was an average pain intensity ≥5 during the last 3 days of the titration period [tramadol/tapentadol PR subgroup, 6.2% (8/129); overall tapentadol PR group, 9.9% (33/335)].

A similar percentage of patients used rescue medication in the tramadol/tapentadol PR subgroup [70.5% (91/129)] and in the overall tapentadol PR group [71.9% (241/335)]. The mean (SD) total daily dose of rescue medication was comparable in the tramadol/tapentadol PR subgroup [12.0 (16.87) mg] and in the overall tapentadol PR group [13.3 (17.41) mg], as was the mean (SD) percent of days with rescue medication use [45.1% (39.44%) vs. 46.3% (39.69%), respectively].

3.3 Safety and tolerability

During the titration period, 50.4% (65/129) of patients in the tramadol/tapentadol PR subgroup and 50.0% (169/338) of patients in the overall tapentadol PR group reported ≥1 TEAE. Gastrointestinal and nervous system TEAEs were the most commonly reported TEAEs (incidence ≥5%) during the titration period, and incidences of these TEAEs were generally comparable in the tramadol/tapentadol PR subgroup and in the overall tapentadol PR group (Table 4).

4. Discussion and conclusions

Opioid analgesics have an established role in the management of moderate to severe cancer pain (Droney and Riley, 2009; Caraceni et al., 2012). Morphine has typically been considered the first-line analgesic option for patients with moderate to severe cancer pain (Droney and Riley, 2009; Caraceni et al., 2012) and, along with other opioid analgesics, has a long-

Table 4 Individual TEAEs reported for ≥5% of patients in the tramadol/tapentadol PR subgroup or the overall tapentadol PR group during the titration period (safety populations titration).

System organ class, n (%) TEAE, n (%)	Tramadol/ tapentadol PR subgroup (n = 129)	Overall tapentadol PR group (n = 338)
Gastrointestinal disorders	39 (30.2)	100 (29.6)
Constipation	20 (15.5)	48 (14.2)
Nausea	13 (10.1)	42 (12.4)
Vomiting	5 (3.9)	18 (5.3)
Nervous system disorders	21 (16.3)	46 (13.6)
Somnolence	9 (7.0)	14 (4.1)
Dizziness	8 (6.2)	17 (5.0)

TEAE, treatment-emergent adverse event; PR, prolonged release.

standing history of clinical use for cancer pain management (Droney and Riley, 2009; Caraceni et al., 2012). Morphine and other opioids are often associated with poor, particularly gastrointestinal, tolerability in patients with cancer pain (Droney and Riley, 2009), and opioid-induced gastrointestinal side effects may prove particularly problematic for these patients (Mandala et al., 2006; Droney et al., 2008; Caraceni et al., 2012). In patients who need to switch from a WHO step 2 (e.g. tramadol) to a WHO step 3 analgesic due to worsening pain, tapentadol PR, which has demonstrated improved gastrointestinal tolerability compared with morphine CR (Kress et al., 2014) and oxycodone CR (Imanaka et al., 2013) in cancer pain patients, may be a favourable option.

In this phase 3 cancer pain study, the majority of patients who were pretreated with the WHO step 2 analgesic tramadol before randomization, who were dissatisfied with that treatment for any reason, and who had a pain intensity score ≥5 (11-point NRS) experienced improvements in efficacy after switching to the WHO step 3 analgesic tapentadol PR (100–250 mg bid). Responder rates during the titration period for this subgroup of patients who were pretreated with the WHO step 2 opioid tramadol were high (approximately 70%), and the tolerability profile was similar to the overall tapentadol PR group. Thus, based on the responder criteria, the majority of tramadol-pretreated patients were able to complete treatment with tapentadol PR during the titration period and experienced a reduction in pain intensity to <5 by the end of the titration period, without the need for excessive rescue medication.

Analgesic efficacy during the titration period for this subgroup of tramadol-pretreated patients who switched to tapentadol PR was generally comparable to that for the overall population of patients who received tapentadol PR during the titration period of the randomized, controlled phase 3 study (Kress et al., 2014). On average, doses of tapentadol PR used in the tramadol/tapentadol PR subgroup were comparable to those used in the overall tapentadol PR group. Importantly, tapentadol PR was generally well tolerated in this subgroup of patients switching from tramadol (a WHO step 2 opioid) to tapentadol PR (a WHO step 3 analgesic), with a similar tolerability profile to the overall tapentadol PR group during titration. These results indicate that efficacy and tolerability were similar for a subgroup of patients who were pretreated with tramadol prior to randomization to tapentadol and the overall tapentadol PR group. It should be noted that comparisons between the tramadol/tapentadol PR subgroup and overall tapentadol PR group were descriptive. No formal statistical analyses were performed to compare the data for the tramadol/tapentadol PR subgroup and the overall tapentadol PR group.

Results of this present subgroup analysis suggest that patients who need to switch from the WHO step 2 analgesic tramadol for any reason (e.g. inadequate pain relief) can safely be converted directly to the WHO step 3 analgesic tapentadol PR for improved analgesic therapy for severe pain.

Author contributions

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Average pain intensity scores during the titration period and change in average pain intensity from the start of titration (full analysis populations-titration).