SENSITIVITY OF ALLODYNIA AREA COMPARED WITH INTENSITY IN DETECTING EFFECTS OF A NOVEL ANALGESIC GRT6010 IN PERIPHERAL NEUROPATHIC PAIN PATIENTS

5-0617

Presented at the 9th Congress of the European Pain Federation EFIC
Vienna, Austria
2–5 September 2015

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BACKGROUND AND AIMS

- Quantitative sensory testing (QST) assessments can be valuable tools in analgesic research although there are few studies that directly compare the sensitivity of different techniques. This is particularly important given that the pain research literature reportedly contains a relatively large number of publications where authors attempt to selectively emphasise certain results (Gewandter et al. 2015)
- This analysis compares the relative sensitivity of the 128 mN pinprick and standardised brush tests (used to measure static and dynamic allodynia area, respectively) with measurements of mechanical pain sensitivity (MPS) and dynamic mechanical allodynia (DMA) intensity using standard QST procedures
- The tests were carried out as part of a Phase IIa clinical trial comparing GRT6010, a novel analgesic compound, with pregabalin and placebo in 57 subjects with peripheral neuropathic pain

METHODS

This was a randomised, multi-centre, double-blind, double-dummy, active- and placebo-controlled, parallel group, multiple oral administration Phase IIa trial. It was conducted according to Good Clinical Practice guidelines and approved by independent ethics committees. The pain sensitivity measurements discussed here were conducted at Baseline and on Days 6 and 7 of treatment.

Day	-28	…	-4	-3	-2	-1	1				5	6	7			10	…	36
	Hospitalisation																	
	Washout						Treatment								Follow up			
				Baseline							End-of-treatment							
Tests					X	X						X	X					

Treatment arms

- GRT6010 (6 mg on Day 1; 0.6 mg on Days 2–7) and placebo for pregabalin
- Pregabalin (2x75 mg on Days 1–3; 2x150 mg on Days 4–7) and placebo for GRT6010
- Placebo for both GRT6010 and pregabalin

Paracetamol up to 3 g/day was available for use as rescue medicine only outside the baseline and end-of-treatment pain evaluation periods.

Key inclusion criteria

- Subjects aged 18 to 75 years
- Presence of persistent “probable” or “definite” (Treede et al. 2008) peripheral neuropathic pain for at least 6 months due to modified radical mastectomy, breast conserving surgery, cosmetic breast surgery, lateral and postero-lateral thoracotomy, post-herpetic neuralgia or traumatic nerve lesions of upper or lower limb
- Intensity of dynamic mechanical allodynia on the affected side greater than 20 (0–100 Numeric Rating Scale [NRS]), or increased mechanical pain sensitivity
- An average ongoing pain intensity score of more than 4 and less than 9 (0–10 NRS) within the 3 day Baseline period

Key exclusion criteria

- Presence of clinically relevant disease as defined by the trial protocol
- Presence of confounding pain conditions
- Presence of exclusively negative symptoms of neuropathic pain

Outcome measures

- Change in area of static allodynia from Baseline to end of treatment according to 128 mN pinprick test
- Change in area of dynamic allodynia from Baseline to end of treatment according to standardised brush test
- Change in mechanical pain sensitivity from Baseline to end of treatment
- Change in dynamic mechanical allodynia intensity from Baseline to end of treatment

Static and dynamic allodynia area determination

A point lying in the centre of the area of maximum pain was marked with a skin marker. Stimulation using an 128 mN pinprick stimulus (static allodynia) or gentle stroking with a standardised brush (dynamic allodynia) began distant from this point and was applied at 1 cm intervals moving towards the area of maximum pain along each of eight directional planes until the point where the subject reported an unpleasant or painful sensation. Areas of static and dynamic allodynia were calculated using the individual measurements from the centre for each of the eight lines.

Quantitative sensory testing

Quantitative sensory testing is a defined procedure to assess somato-sensory functions (Rolke et al. 2006). Subtests of quantitative sensory testing for stimulus/response-functions (MPS for pinprick stimuli and DMA) were used. The tests were applied to the area of maximal pain intensity as indicated by the subject (affected side) and to the contralateral site (control side).

Mechanical pain sensitivity

Seven, weighted pinprick stimuli (exerting forces of 8, 16, 32, 64, 128, 256 and 512 mN) were used to obtain the stimulus-response function for pinprick-evoked pain. The stimulators were applied at a rate of 2 seconds on and 2 seconds off. Subjects were asked to give a pain rating for each stimulus on a 0–100 numeric rating scale (NRS; “0” indicating “no pain”, and “100” indicating “most intense pain imaginable”). Mechanical pain sensitivity was calculated as the geometric mean of all numerical ratings for pinprick stimuli.

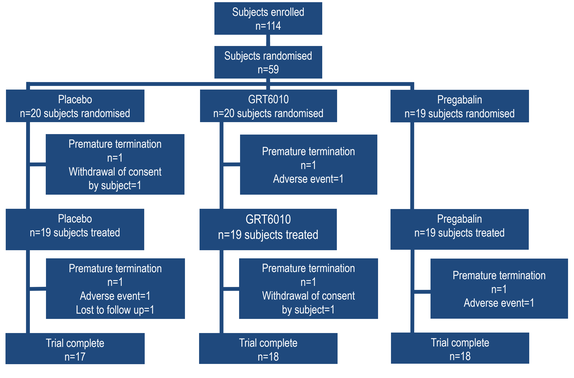
Dynamic mechanical allodynia

A set of three light tactile stimulators were used as moving innocuous stimuli:

- Cotton wisp exerting a force of approximately 3 mN
- Cotton wool tip fixed to an elastic strip exerting a force of approximately 100 mN
- Standardised brush exerting a force of approximately 200 mN to 400 mN

The tactile stimuli were applied with a single stroke of approximately 2 cm in length over the skin in between the pinprick stimuli (five repetitions), so that a total of 50 stimuli (15 tactile and 35 pinpricks) were delivered at both the affected and the contralateral site with the subject giving numerical pain ratings for each stimulus. Dynamic mechanical allodynia was calculated as the geometric mean of all numerical ratings across all three different types of light touch stimulators.

RESULTS



Disposition of subjects

The study enrolled 114 subjects and 19 subjects were randomised into each of the three treatment arms. One subject in each group discontinued the trial during the treatment phase (Placebo group, Day 6 of treatment, hypersomnia; GRT6010 group, Day 7 of treatment, withdrawal of consent; Pregabalin group, Day 5 of treatment, increase in liver enzyme levels).

		Placebo	GRT6010	Pregabalin	Overall
Intent-to-treat set	**N (%)**	19 (100)	19 (100)	19 (100)	57 (100)
Sex	Male N (%)	7 (36.8)	8 (42.1)	7 (36.8)	22 (38.6)
	Female N (%)	12 (63.2)	11 (57.9)	12 (63.2)	35 (61.4)
Age (years)	Mean±SD	46.53±14.83	54.00±9.93	50.53±14.55	50.35±13.41
	Min–Max	23–68	36–72	26–74	23–74
Body mass index (kg/m²)	Mean±SD	27.56±3.80	27.37±3.03	27.27±3.32	27.40±3.34
Time since diagnosis (months)	Median	29	79	45	40
Peripheral nerve injury	N (%)	0 (0.0)	0 (0.0)	1 (5.3)	1 (1.8)
Breast/thoracic surgery	N (%)	4 (21.1)	3 (15.8)	6 (31.6)	13 (22.8)
Post-herpetic neuralgia	N (%)	15 (79.9)	16 (84.2)	12 (63.1)	43 (75.4)
Presence of neuropathic pain:					
“definite”	N (%)	4 (21.1)	8 (42.1)	3 (15.8)	15 (26.3)
“probably”	N (%)	15 (78.9)	11 (57.9)	16 (84.2)	42 (73.7)

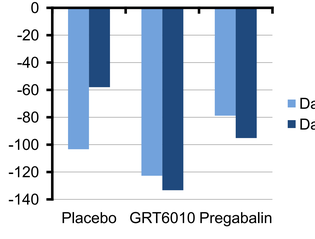
N, number of subjects; SD, standard deviation

The treatment groups were similar with respect to most baseline characteristics. The subjects in the GRT6010 group had a higher mean age (54.00±9.93 years) than the Placebo (46.53±14.83 years) and Pregabalin (50.53±14.55 years) groups. Mean time since diagnosis of neuropathic pain was longer in the GRT6010 group (79 months) than in the Placebo (29 months) and Pregabalin (45 months) groups.

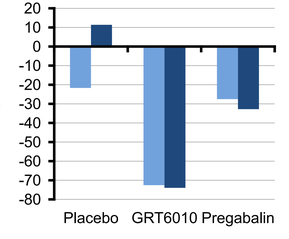
Treatment with GRT6010 and pregabalin but not placebo decreased the area of static allodynia compared with baseline after 7 days

The mean (SD) change in area of static allodynia at Day 7 from Baseline was -58.01 (415.29) cm² in the Placebo group, -133.29 (228.58) cm² in the GRT6010 group, and -95.16 (108.04) cm² in the Pregabalin group.

Change in area of static allodynia (cm²) from Baseline to Day 6 or 7 of treatment



Change in area of dynamic allodynia (cm²) from Baseline to Day 6 or 7 of treatment



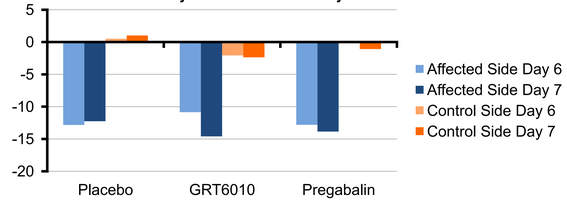
Treatment with GRT6010 and pregabalin but not placebo decreased the area of dynamic allodynia compared with baseline after 7 days

The mean (SD) change in area of dynamic allodynia at Day 7 from baseline was 11.36 (153.96) cm² in the Placebo group, -73.98 (149.54) cm² in the GRT6010 group, and -32.78 (75.96) cm² in the Pregabalin group.

Mechanical pain sensitivity improved on the affected side in all three treatment groups

Using a 0–100 numeric rating scale, the mean (SD) change from baseline at Day 7 was -12.26 (23.28) in the placebo group, -14.60 (17.79) in the GRT6010 group, and -13.86 (15.32) in the pregabalin group. Mechanical pain sensitivity (0–100 NRS) was minimal on the contralateral side in all three treatment groups with minimal change from baseline at Day 6 and Day 7.

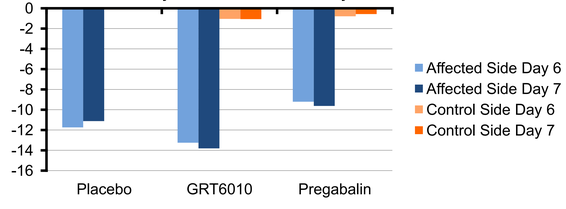
Change in intensity on 0–100 scale of mechanical pain sensitivity from Baseline to Day 6 or 7 of treatment



Dynamic mechanical allodynia improved on the affected side in all three treatment groups

Using a 0–100 numeric rating scale, the mean (SD) change from baseline at Day 7 was -11.12 (17.49) in the placebo group, -13.81 (19.81) in the GRT6010 group, and -9.63 (13.00) in the pregabalin group. Dynamic mechanic allodynia was minimal on the contralateral side in all three treatment groups with minimal change from baseline at Day 6 and Day 7.

Change in intensity on 0–100 scale of dynamic mechanical allodynia from Baseline to Day 6 or 7 of treatment



CONCLUSIONS

- Area mapping appears to be more sensitive than MPS/DMA in detecting the effects of GRT6010. This may be due to the clearer signal produced by these measurements and the fact that they do not rely on a subjective NRS assessment
- Sensitivity was also improved for pregabalin which, despite having clinically established efficacy, was not shown to be different from placebo by the NRS-based methods
- The consistency between the two sets of pre/post-dose values suggests good test-retest validity for all endpoints

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ClinicalTrials.gov identifier: NTC01485094