Brief Communication

A clinical study to compare the efficacy and safety of pregabalin sustained release formulation with pregabalin immediate release formulation in patients of diabetic peripheral neuropathic pain

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ABSTRACT

Objective: To compare the efficacy and safety of sustained release (SR) formulation of pregabalin with immediate release (IR) formulation in patient with diabetic peripheral neuropathic pain. **Materials and Methods:** In this open label, randomized, comparative, multicentric study, the primary efficacy measure was reduction in visual analogue scale (VAS) of short form McGill pain questionnaire (SF-MPQ) score from baseline to last visit. The secondary evaluation measures included reduction in SF-MPQ descriptive score and present pain intensity score and change in clinical global impression - improvement of illness (CGI-I) and clinical global impression - severity of illness (CGI-S) from baseline to last visit. Total duration of the study was 12 weeks. Safety evaluation was done by recording treatment emergent adverse events and laboratory investigations at baseline and end of treatment. **Results:** Of 265 randomized patients, 133 received pregabalin SR tablets and 132 pregabalin IR. Patients randomized to both treatments responded to respective treatments. The least square means of VAS score in both the groups were reduced significantly (P <0.01). Reduction in both groups was similar (P = ns). At the end of the trial in both the groups, there was a significant reduction in the SF-MPQ descriptive score (P <0.01), severity of illness as well as clinically significant improvement in the symptoms. Difference between the groups for CGI-I (P = 0.37) and CGI-S (P = 0.41) score was not statistically significant. Treatment in both the groups was found safe and well tolerated. **Conclusion:** The study shows that the pregabalin SR is safe and effective in patients of diabetic peripheral neuropathic pain. The results of the study demonstrated that pregabalin SR has comparable efficacy and safety as pregabalin IR.

Key words: Immediate release formulation, pregabalin, sustained release formulation

Introduction

Pregabalin has attained widespread use in the treatment of painful diabetic peripheral neuropathy.[1] The objective of this research was to analyze the clinical profile of Pregabalin immediate release (IR) *vs* sustained release (SR) in a real world setting.[2] This is the first study which explores whether pregabalin SR tablets maintain the required therapeutic concentration with less peak trough fluctuations and prolongs the release of pregabalin.

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Materials and Methods

This was an open-label, randomized, parallel, comparative, multicentric study. After successful screening and enrollment, patients were given trial medication for one week followed up at visit 2 (end of 1st week), visit 3 (end of 3rd week), visit 4 (end of 6th week), visit 5 (end of 9th week), and visit 6 (end of 12th week). Thus, total duration of the treatment was 12 weeks per patient.

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Patients satisfying inclusion and exclusion criteria were allocated any of the two treatments as per randomization schedule. The baseline efficacy parameter assessment was done on the first day of active treatment phase (Day-1, Visit-1). After one week, patients were evaluated as responders or non-responders based on the scores on VAS (Visual Analogue Scale) of SF-MPQ (Short Form McGill Pain Questionnaire). Responders were the ones whose pain reduction on the VAS score was ≥30%. For non-responders, dose escalation was done. The patients randomized to treatment-pregabalin SR received 150 mg once daily for 1 week. After 1 week of treatment, the non-responders were up-titrated to 300 mg once daily and the responders continued the same dose. Similarly, in the Pregabalin IR group, initially the patients received 75 mg twice daily for 1 week followed by 150 mg BID for rest of the period (for non-responders). Patients were evaluated for safety by recording adverse events and laboratory investigations at the baseline and end of the treatment.

Inclusion criteria

Enrolled patients were male or female aged ≥18 and <70 years, with diagnosis of diabetic neuropathic pain (Type I and II) having HbA1c levels of ≤10% and having a score of >30 mm on the VAS of SF-MPQ. Patients who had not taken any analgesics except paracetamol for symptomatic relief of pain for last 10 days were included.

Objective:

Primary objective was to compare the safety of SR formulation in comparison to IR formulation without compromising efficacy.

Primary efficacy variables

The primary efficacy evaluation criterion was the reduction in VAS of SFMPQ score from baseline to last visit in both treatment arms:

- Numeric scale of 0-100 mm represents the VAS for no pain to worst possible pain.

Secondary efficacy variables

a) Reduction in Sensory dimension pain scores from baseline to last visit in both treatment arms:
   - Descriptors (1-11) from SFMPQ represents the sensory dimension of pain on an intensity scale of 0 = none, 1 = mild, 2 = moderate, 3 = severe.

b) Reduction in Affective dimension pain scores from baseline to last visit in both treatment arms:
   - Descriptors (12-15) from SFMPQ represents the affective dimension of pain on an intensity scale of 0 = none, 1 = mild, 2 = moderate, 3 = severe.

c) Reduction in PPI scores from baseline to last visit in both treatment arms:
   - Percentage frequency were derived for severity of PPI Scores described as 0 = No pain, 1 = Mild, 2 = Discomforting, 3 = Distressing, 4 = Horrible, 5 = Excruciating.

d) Change in Clinical Global Impression-Severity Scale (CGI-S) from baseline to last visit in both treatment arms:
   - Percentage frequency were derived for severity of CGI Scores as 0 = Not Assessed, 1 = Normal, Not ill At All, 2 = Borderline Mildly ill, 3 = Mildly ill, 4 = Moderately ill, 5 = Markedly ill, 6 = Severely ill, 7 = Among The Most Extremely ill Patients.

e) Change in Clinical Global Impression-Improvement Scale (CGI-I) from baseline to last visit in both treatment arms:
   - Percentage frequency were derived for improvement of CGI Scores as 0 = Not Assessed, 1 = Very Much Improved, 2 = Much Improved, 3 = Minimally Improved, 4 = No Change, 5 = Minimally Worse, 6 = Much Worse, 7 = Very Much Worse.

Safety measures

Safety and tolerability were evaluated by adverse event monitoring. Laboratory tests assessment was carried out for all the patients at baseline and at the end of the trial.

Results

Patient disposition

Of 265 randomized patients, 47 patients were dropped from the study. Twenty-seven patients were lost to follow up, six patients were withdrawn due to suspected adverse reactions, 10 patients requested to withdraw, three patients were withdrawn due to poor compliance, and one patient was withdrawn due to other reasons.

Primary efficacy endpoints

VAS of SFMPQ score

There was a statistically significant reduction within the treatment group observed from baseline to end of trial (week 12) (P <0.01, for both the treatment groups). However, there were no statistically significant difference (P = 0.36) in efficacy between two treatment groups.

Secondary efficacy endpoints

There were statistically significant reduction in score for all secondary efficacy parameters (P <0.01) like sensory dimension pain of SFMPQ and affective dimension pain of SFMPQ for both the treatment group. The difference between treatment group for secondary efficacy parameters (sensory dimension pain of SFMPQ [P = 0.25], affective dimension pain of SFMPQ [P = 0.99], present pain

intensity of SFMPQ [P = 0.20], CGI-I [P = 0.41], and CGI-S [P = 0.37]) were not significant statistically. At visit 2, there was a statistically significant difference in reduction (P <0.01) in affective dimension of pain scores from baseline observed between groups.

Response analysis

Patients were considered as responders if there is at least 30% reduction in visit 2 VAS score compared to visit 1. Number of responders in Pregabalin SR group was 81% and in Pregabalin IR group was 75%.

Safety and tolerability

All the patients enrolled in the trial had laboratory parameters within normal range or were clinically not significant according to investigators assessment during screening and at the end of the trial. There were three unexpected serious adverse event reported during the trial in Pregabalin IR treatment group. The adverse events reported were serious, not expected, and unrelated with the study drug. Total 40 AEs were reported during trial. All reported AEs were mild, moderate, or severe in nature in both treatment groups. Both the drugs were well tolerated with 10.4% patients reporting AEs in Pregabalin SR group and 8.66% patients reporting AEs in Pregabalin IR group.

Discussion

In the primary efficacy parameter, both the treatment groups showed statistically significant reduction from baseline to end of trial (week 12) (P <0.01).

There was statistically significant reduction in score from the baseline for all secondary efficacy parameters for both the treatment groups. However, the difference between treatment groups for secondary efficacy parameters was not statistically significant. Pregabalin SR and Pregabalin IR offered comparable benefits in the pain reduction as assessed by CGI-Severity and CGI-Improvement scales. Both the groups have shown comparable safety in the study.

Conclusion

This study indicates that pregabalin SR is effective in relieving diabetic peripheral neuropathic pain as well as exhibits acceptable safety and tolerability profile. Both pregabalin SR and pregabalin IR are equally efficacious for the treatment of diabetic peripheral neuropathic pain. Thus, pregabalin SR has the potential to be a useful new treatment option for patients with diabetic peripheral neuropathic pain. Administration of pregabalin SR once daily will ensure better patient compliance during therapy.

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References

1. Freeman R, Durso-Decruz E, Emir B. Efficacy, safety, and tolerability of pregabalin treatment for painful diabetic peripheral neuropathy. Diabetes Care 2008;31:1448-54.
2. Navarro A, Saldaña MT, Pérez C, Torrades S, Rejas J. A cost-consequences analysis of the effect of Pregabalin in the treatment of peripheral Neuropathic Pain in routine medical practice in Primary Care settings. BMC Neurol 2011;11:7.

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