Efficacy of Calcitonin Gene-Related Peptide Antagonists in the Treatment of Acute Migraine: A Systematic Review and Meta-analysis

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ABSTRACT

Objective. This study determined the efficacy of calcitonin gene-related peptide (CGRP) antagonists in the treatment of acute migraine.

Methods. Seven randomized, controlled trials were included. Outcome measures used were pain freedom and pain relief two hours after treatment.

Results. The difference in pain freedom 2 hours post-dose significantly favored gepants 140/150 mg (OR=2.39, 95% CI=1.93-2.96, P<0.00001) and 280/300 mg (OR=2.94, 95% CI=2.44-3.35, P<0.00001) over placebo, while the difference in pain freedom 2 hours post- dose did not significantly favor triptans over gepants 140/150 mg and vice versa (OR=0.62, 95% CI=0.32-1.21, P=0.16) and over gepants 280/300 mg (OR=0.86, 95% CI=0.64-1.15, P=0.34). The difference in pain relief 2 hours post-dose significantly favored gepants 140/150 mg (OR=2.49, 95% CI=2.13-2.91, P<0.00001) and 280/300 mg (OR=2.78, 95% CI=2.41-3.21, P<0.00001) over placebo. The difference in pain relief 2 hours post-dose significantly favored triptans over gepants 140/150 mg (OR=0.73, 95% CI=0.56-0.96, P=0.03), but not over gepants 280/300 mg and vice versa (OR=0.98, 95% CI=0.76-1.27, P=0.89).

Conclusion. With regard to pain freedom and pain relief two hours post-dose, CGRP antagonists are more efficacious than placebo in the treatment of acute migraine but there is insufficient evidence to demonstrate superior efficacy of CGRP antagonists over triptans.

Key Words: Calcitonin gene-related peptide, migraine, triptans, pain

INTRODUCTION

Migraine is defined by the International Headache Society as recurrent head pain, usually unilateral and pulsating, associated with nausea and or vomiting, moderate to severe in intensity that lasts for 4-72 hours, which may or may not be preceded by visual, sensory or motor symptoms[1]. For the past 25 years, it has consistently been included in the leading causes of disability among neurological disorders worldwide. According to an analysis of the Global Burden of Disease Survey from 1990 to 2013, migraine has consistently been in the top ten causes of disability in the world, usually in the sixth or seventh place. In the Philippines it ranks sixth behind diabetes in the top ten causes of years lived with disability[2,3,4]. Current therapeutic options for migraine are serotonin agonists or triptans, ergot alkaloids, and nonsteroidal anti-inflammatory agents. However, these interventions are not effective in all individuals and there is a continuing need for new agents that are more specific for the pathophysiology of migraine[5,6].

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More than 20 years ago, the role of calcitonin gene-related peptide (CGRP) in migraine was established. This 37-amino acid neuropeptide discovered in 1982 causes arteriolar vasodilation, specifically triggered by trigeminal nerve activation and was shown to be increased in both peripheral and cranial circulation during migraine episodes. Subsequently, CGRP levels declined when anti-migraine medications were administered or when the episodes have abated. This discovery paved the way to the concept of using CGRP antagonists as potential treatment for migraine as this disease continues to be a global concern[7,8,9].

So far, there are at least five CGRP antagonists that have demonstrated efficacy in the acute treatment of migraine, and these are the following: olcegepant (BIBN4096), telcagepant (MK-0974), MK-3207, BI 44370 TA, and BMS-927711. Several Phase II and Phase III trials have shown the efficacy and tolerability of these antagonists compared with placebo, as well as with triptans[10]. There are quite a number of meta-analyses available on the individual CGRP antagonists developed so far. However, there are still no studies available that have analyzed these antagonists as a group.

This systematic review and meta-analysis aimed to analyze existing data on CGRP antagonists as a group and to determine their efficacy as compared with placebo and with triptans.

MATERIALS AND METHODS

This meta-analysis followed the recommendations and standards set by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

A. Data Source

This study aimed to retrieve all articles on the treatment efficacy of calcitonin-related gene peptide receptor antagonists on acute migraine. Two independent physician researchers conducted a thorough search of major bibliographic databases, as follows: PubMed MEDLINE, Cochrane Central, EMBASE, Google Scholar, APAMED Central, and Western Pacific Region Index Medicus from study conceptualization until September 21, 2015. For each database, no limits were set for year of publication; the earliest possible year of publication was included. These databases were accessed locally. Search strategies were defined using Medical Subject Heading (MeSH) terms "migraine disorder", "telcagepant", and free text terms “migraine”, "calcitonin-related gene peptide", "CGRP receptor antagonists", "efficacy", "randomized control trial", "meta-analysis" and a combination of these terms (Table 1). The researchers also registered with PubMed My NCBI for these key search phrases. Both ancestor and descendant search strategies were employed. Manual search of reference list of systematic reviews and meta-analyses was done. Different authors were emailed for clarifications or reprint requests as deemed necessary. Local and international expert opinion was sought. Published articles on human subjects and in the English language are the ones included.

Table 1. Search strategy used to identify studies on CGRP antagonists and migraine

Medical subject heading (MeSH) terms and free text terms search
1. “migraine disorder”
2. “migraine”
3. “calcitonin-gene related peptide”
4. “CGRP receptor antagonists”
5. “telcagepant”
6. “randomized control trial”
7. “meta analysis”
8. “(1) OR (2)”
9. “(3) OR (4)”
10. “(8) AND (9) AND (5)”
11. “(10) AND (6)”
12. “(11) AND (7)”

B. Study Selection

Preliminary screening of study abstracts was done by the primary investigators to check if the articles dealt with the following: adult patients 18 years old and above; patients with history of migraine, moderate to severe as defined by the International Headache Society criteria; treatment intervention used was to address acute migraine; randomized controlled design; comparisons of treatment intervention to placebo or an active comparator group; outcomes included pain freedom and pain relief 2 hours post-dose; and if these studies contained specific effect estimates such as odds ratios, risk ratios, or hazards ratios. Identified citations were then tabulated in a Microsoft Excel 2007 spreadsheet and full text articles were retrieved. These articles were appraised for inclusion according to a pre-specified inclusion criterion. The final set of qualified articles for the meta-analysis was then subjected to quality scoring and data extraction by the primary investigators.

C. Data Extraction and Risk of Bias Assessment

Data extraction was performed using standard data retrieval sheet. For each included eligible study, detailed information on the study design, last name of first author, date of publication, journal of publication, number of study participants enrolled, number of study participants evaluated, type of CGRP receptor antagonist and dosage(s), type of comparator (placebo, active comparator), route of administration, population demographics (age and sex distribution), outcomes (pain freedom and pain relief), estimated size of effects, and confidence intervals were obtained. To assess the quality of the studies and risk of bias, at least two authors assessed the included studies using the Risk of Bias (RoB) tool as recommended by the Cochrane Handbook of Systematic Review of Interventions (Version 5.1.0). If there was a discrepancy in the quality scoring, discussions were done until consensus was reached.

Table 2. Characteristics of studies included in the meta-analysis

Author, Year	Gepant		Triptan		Placebo	Outcomes
	N	Dose (mg)	N	Dose (mg)	N	
Ho et al. (2008)	687	150, n= 333 300, n=354	345	5	348	Pain freedom after 2 hours treatment, pain relief after 2 hours treatment
Ho et al. (2008)	39	300, n= 39	34	10	115	Primary endpoint: pain relief (reduction to mild to none) 2 hours after dosing
						Secondary endpoint: pain freedom at 2 hours and sustained pain relief at 24 hours
Connor, et al. (2009)	500	50, n=177 150, n=381 300, n=371	-	-	365	Co-primary endpoints: pain freedom, pain relief, and absence of photophobia, absence of phonophobia, and absence of nausea, all at 2 hours post-dose
						Secondary endpoint: 2-24 hours sustained pain freedom
Ho et al. (2010)	1122	140, n= 573 280, n= 549	-	-	555	Primary endpoints: 2-hour pain freedom, 2-hour pain relief, 2-hour absence of migraine-associated symptoms (phonophobia, photophobia, nausea), and 2-24 hours sustained pain freedom
Hewitt et al. (2011)	416	280, n= 138	-	-	147	Primary endpoint: 2-hour pain freedom
Ho et al. (2011)	52	300, n= 52	-	-	53	Primary endpoint: 2-hour pain freedom
Marcus, et al. (2014)	547	10, n= 85 25, n= 68 75, n= 91 150, n= 90 300, n= 121 600, n= 92	109	100	229	Primary endpoints: pain freedom at two hours post dose
						Secondary endpoint: sustained pain-freedom from two to 24 hours post dose

D. Outcome Measures

The primary outcomes were pain freedom and pain relief two hours post-dose. Pain freedom was defined as resolution of pain from severe or moderate to no pain. Pain relief was defined as decrease in severity of pain from severe to moderate or moderate to mild or no pain.

E. Statistical Analysis

A comparison between study participants was done per primary outcome (pain freedom and pain relief at 2 hours post-dose) to those treated with CGRP receptor antagonist/ gepants versus placebo and CGRP receptor antagonist/ gepants versus zolmitriptan or rizatriptan (triptans). A Chi^2 test was utilized to determine homogeneity and I^2. Fixed-effects model was used when heterogeneity was not significant (I^2<50%), otherwise, random-effects model of analysis was applied. Odds ratio with 95% confidence interval was calculated for each study and the study comparisons. Test for overall effect was also measured for all the studies combined. A funnel plot was used to measure potential publication bias. Review Manager statistical software version 5.3.5 was used for all analyses (Cochrane Review).

RESULTS

A. Search Results

A total of 1398 articles were identified by titles and abstracts, with duplicates removed. Among the 1398 articles that were identified, 1376 studies were excluded since they did not measure effect estimates of interest. The remaining 21 articles were screened for detailed assessment; three studies were excluded because they had different routes of administration for the CGRP receptor antagonists, while seven studies had different primary outcomes of interest, and one study was terminated due to adverse events, whereas two were meta-analyses. Eight full-text articles were assessed for eligibility, of which one study did not contain a compatible dosage preparation of interest. A total of seven studies were included in the final meta-analysis (Figure 1). Of the seven studies, Marcus et al. has not been cited in previous meta-analyses.

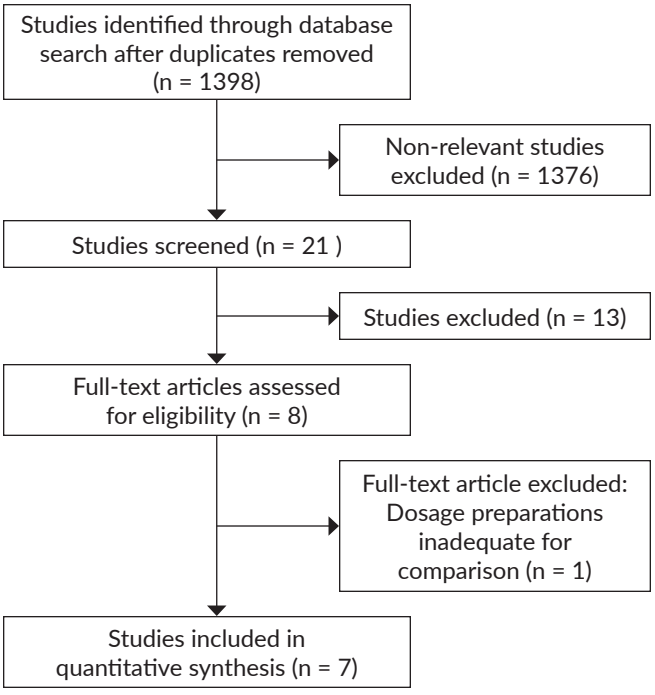

Figure 1. Flow diagram of study selection.

B. Meta-analysis

Effect estimates of efficacy of calcitonin-related gene peptide receptor antagonists on acute treatment of migraine from different studies were pooled for meta-analysis. The seven studies used to estimate efficacy provided data on number of events, number of patients treated, and mean standard deviation (SD). To check for accuracy of data, pertinent data were extracted independently by two reviewers from each study and comparisons of results were done.

In pooling the estimates, a homogeneity test was performed. When the hypothesis of homogeneity of studies was not rejected, it was assumed that the individual effect estimates came from the same population and that each study was estimating an effect estimate that was constant across the studies. Therefore, a fixed-effects model could be used to come up with the pooled estimate. If the hypothesis of homogeneity was rejected, a random-effects model was used to project a pooled estimate.

C. Outcome measures

Pain freedom at 2 hours post-dose. The Forest plot in Figure 2 shows comparison of treatments for pain freedom at 2 hours' post-dose between gepants 140/150 mg versus placebo (4 studies included) and gepants 280/300 mg versus placebo (7 studies included). Both comparisons showed homogeneity (gepant 140/150 mg versus placebo; $Chi^2 = 1.04$, $I^2 = 0\%$, P = 0.79; gepant 280/300 mg versus placebo; $Chi^2 = 5.91$, $I^2 = 0\%$, P = 0.43); hence, fixed-effects model was used. The pooled effect estimate for pain freedom 2 hours post-dose significantly favored gepants 140/150 mg (OR = 2.39, 95% CI = 1.93 to 2.96, P <0.00001) and 280/300 mg (OR = 2.94, 95% CI = 2.44 to 3.35, P <0.00001) over placebo.

The Forest plot in Figure 3 shows comparison of treatments for pain freedom at 2 hours post-dose between gepants 140/150 mg versus triptans (2 studies included) and gepants 280/300 mg versus triptans (3 studies included). Comparison between gepants 140/150 mg versus triptans showed substantial heterogeneity, ($Chi^2 = 3.62$, $I^2 = 72\%$, P = 0.06); thus, a random-effects model was used. Comparisons between gepants 280/300 mg versus triptans showed homogeneity, ($Chi^2 = 2.13$ $I^2 = 6\%$, P = 0.34); thus, a fixed-effects model was used. The pooled effect estimates for pain freedom 2 hours post-dose did not favor significantly triptans over gepants 140/150 mg and vice versa (OR = 0.62, 95% CI = 0.32 to 1.21, P = 0.16). Also, pooled effect estimates for pain freedom 2 hours post-dose did not favor significantly triptans over gepants 280/300 mg (OR = 0.86, 95% CI = 0.64 to 1.15, P = 0.34).

Pain relief at 2 hours post-dose. The Forest plot in Figure 4 shows comparison of treatments for pain relief at 2 hours post-dose between gepants 140/150 mg versus placebo (4 studies included) and gepants 280/300 mg versus placebo (7 studies included). Both comparisons showed moderate heterogeneity (gepant 140/150 mg versus placebo; $Chi^2 = 4.89$, $I^2 = 39\%$, P = 0.18; gepant 280/300 mg versus placebo; $Chi^2 = 7.59$, $I^2 = 21\%$, P = 0.21); hence, fixed-effects model was used. The pooled effect estimate for pain relief 2 hours post-dose significantly favored gepants 140/150 mg (OR = 2.49, 95% CI = 2.13 to 2.91, P <0.00001) and 280/300 mg (OR = 2.78, 95% CI = 2.41 to 3.21, P <0.00001) over placebo.

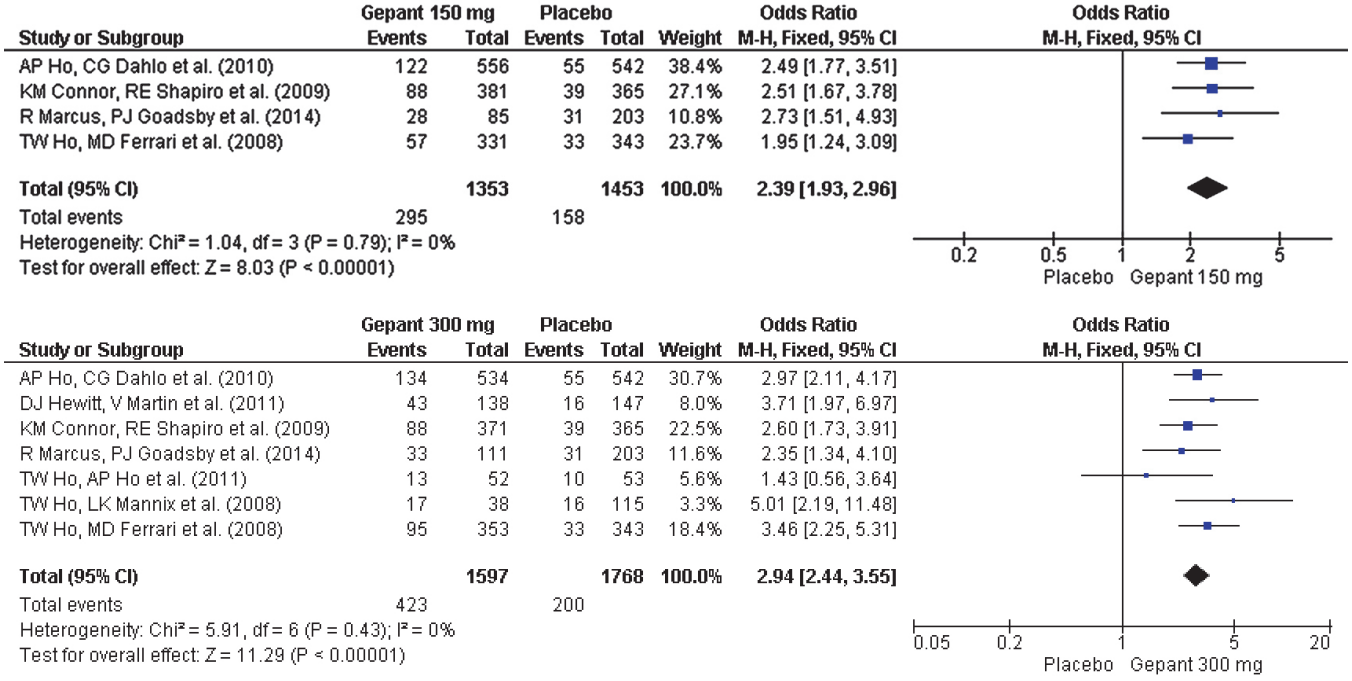

Figure 2. Forest plot comparing treatments (gepants 140/150 mg, 280/300 mg versus placebo) for acute, moderate to severe migraine on pain freedom 2 hours post dose. OR, odds ratio; CI, confidence interval.

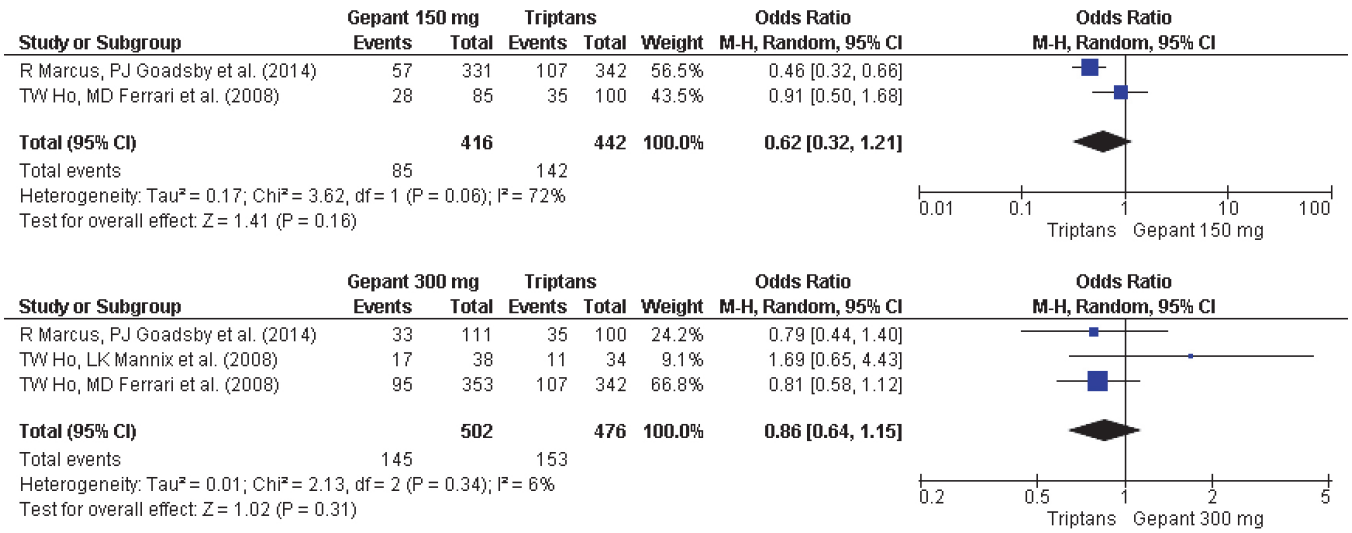

Figure 3. Forest plot comparing treatments (gepants 140/150 mg, 280/300 mg versus triptans) for acute, moderate to severe migraine on pain freedom 2 hours post-dose. OR, odds ratio; CI, confidence interval.

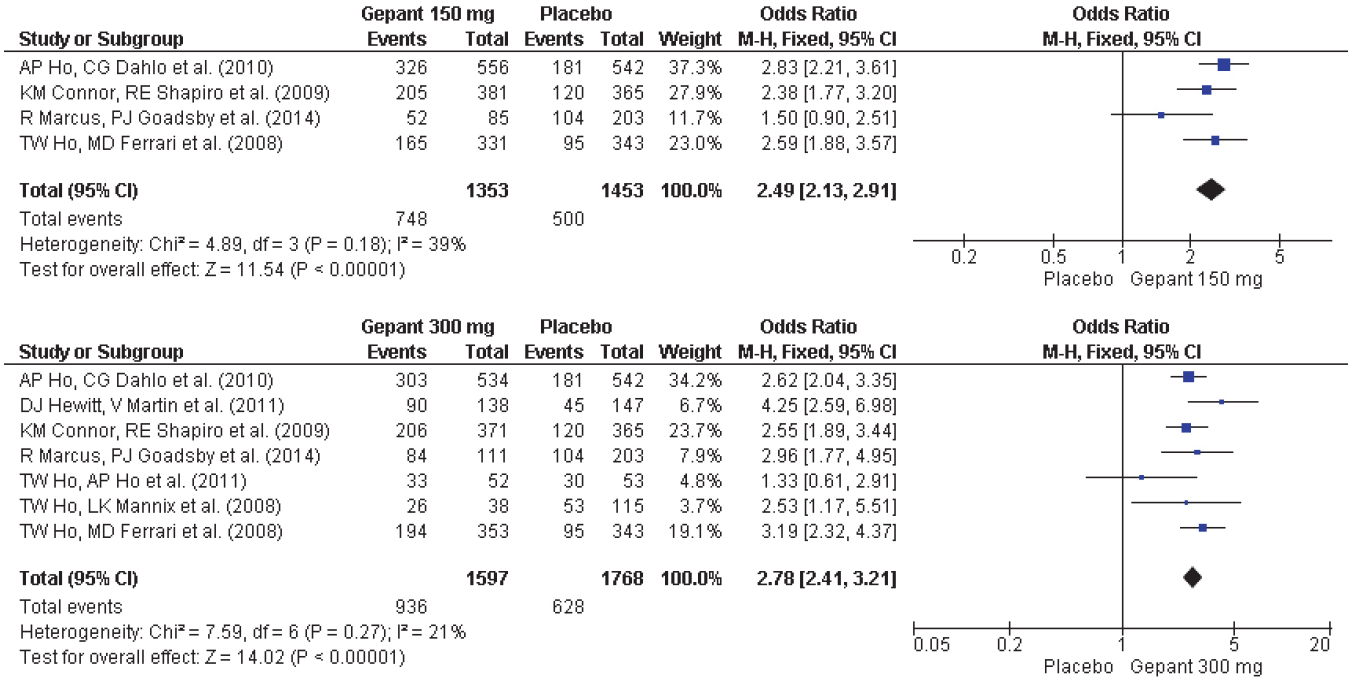

Figure 4. Forest plot comparing treatments (gepants 140/150 mg, 280/300 mg versus placebo) for acute, moderate to severe migraine on pain relief 2 hours post-dose. OR, odds ratio; CI, confidence interval.

The Forest plot in Figure 5 shows comparison of treatments for pain relief at 2 hours post-dose between gepants 140/150 mg versus triptans (2 studies included) and gepants 280/300 mg versus triptans (3 studies included). Comparison between gepants 140/150 mg versus triptans showed homogeneity, (Chi^2 = 0.41, I^2 = 0%, P = 0.52); thus, a fixed-effects model was used. Comparisons between gepants 280/300 mg versus triptans also showed homogeneity, (Chi^2 = 0.54, I^2 = 0%, P = 0.76); thus, a fixed-effects model was used. The pooled estimate effect for pain relief 2 hours post-dose favored significantly triptans over gepants 140/150 mg (OR = 0.73, 95% CI = 0.56 to 0.96, P = 0.03). Meanwhile, pooled effect estimates for pain relief 2 hours post-dose did not favor significantly triptans over gepants 280/300 mg and vice versa (OR = 0.98, 95% CI = 0.76 to 1.27, P = 0.89).

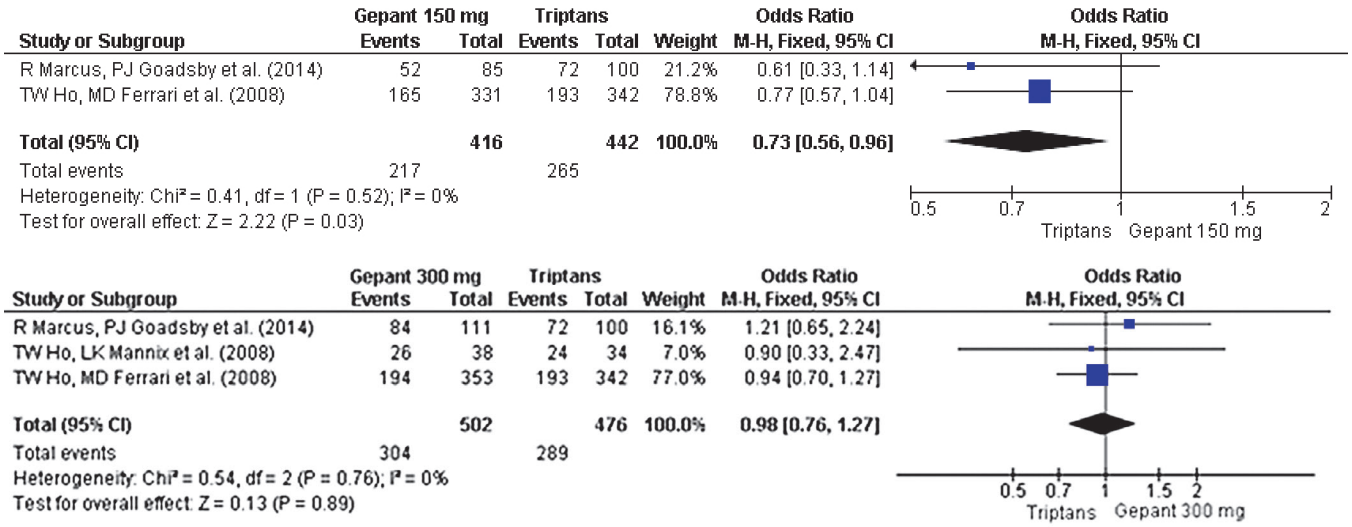

Figure 5. Forest plot comparing treatments (gepants 140/150 mg, 280/300 mg versus placebo) for acute, moderate to severe migraine on pain relief 2 hours post-dose. OR, odds ratio; CI, confidence interval.

DISCUSSION

A. Principal Findings

This meta-analysis examined the efficacy of calcitonin gene-related peptide (CGRP) antagonists with placebo or triptans in the treatment of acute migraine. We extracted data from seven randomized controlled trials that included CGRP antagonists or gepants, specifically telcagepant, BMS-927711, and MK-3207.nOur findings showed that gepants were more efficacious than placebo in treating acute migraine with regard to the outcomes of pain freedom and pain relief two hours post-dose. However, there was limited evidence to demonstrate superior efficacy of gepants over triptans in terms of pain freedom and pain relief two hours post-dose.

Previous meta-analyses available have only compared studies on telcagepant with triptans (zolmitriptan or rizatriptan) while one meta-analysis has compared studies on olcegepant and telcagepant with triptans[11,12]. Our study did not include olcegepant since this is administered intravenously and has limited use in clinical practice[11,13]. Although the individual CGRP antagonists are in different phases of their clinical trials, they are already considered efficacious as treatment for acute migraine. There are also new gepants in development, such as the BI 44370 TA, that are being investigated for efficacy[15]. One meta-analysis, that of Cui et al., has cited that a study on BMS-927711 was still ongoing. Fortunately, the said study had been completed and was included in our meta-analysis. In addition, there is no meta-analysis yet available that has combined the different CGRP antagonists as a class. We deemed it prudent to combine them as a class for this study to establish their efficacy as the next promising treatment in dealing with acute migraine.

The results of this study are consistent with previously published data comparing CGRP antagonists and placebo. The efficacy of CGRP antagonists as treatment for acute migraine lies in the fact that CGRP is at the core of the pathophysiology of this disease. A compound that targets migraine where it starts holds the key to helping the millions around the world who are invariably struck by this debilitating recurrent disease. Currently available treatment, moreso, the gold standard of treatment in acute migraine, the triptans, are continously facing the challenge that many patients still do not respond with the triptans, or could not fully avail of its benefits due to pre-existing cardiovascular diseases that may be exacerbated with the use of such medication[15,16,17,18,19]. Whether or not gepants can heed the call of a treatment that is comparable to or better than the gold standard, current studies may considerably be insufficient but the answers do not seem to be far behind.

To assess for publication bias, a funnel plot was generated but no apparent trend was observed. Although an extensive search was done, there could have been other studies that may not have been published or were unavailable at the time of our search which could have been included for a more conclusive analysis.

B. Limitations of the meta-analysis

The main limitation of this study was the small number of existing studies on the available CGRP antagonists against placebo and/or triptans. As previously mentioned, we only involved studies that used oral preparations of gepants, thereby excluding olcegepant which is administered intravenously. Also, we only involved studies that used the dosages 140mg/150 mg and 280mg/300 mg, as we observed these dosages were mostly the ones consistently present across the available studies. With regard to study outcomes, we dealt only with efficacy "at 2 hours" post-dose; long-term efficacy is beyond the scope of this study. The safety profile

and tolerability of gepants versus triptans were originally sought, however the available studies.

C. Implications for clinical practice

Migraine remains to be in the list of top ten disabling diseases worldwide, causing havoc in an affected person's daily lifestyle and activities. The World Health Organization has even stated that the individual and societal burden of having severe migraine for a day can be as debilitating as being a quadriplegic[5]. Numerous pharmacological options are available in the market but the search for an efficacious drug that will provide pain relief and/or pain freedom for a significant amount of time is still ongoing. The drug class of triptans has been recognized as a pioneer in the treatment of acute migraine, however, numerous patients are still resistant to such drugs and the use of triptans pose a major concern for the increasing number of patients with co-existing cardiovascular diseases. Although it has also been reported in previous meta-analyses and randomized, controlled trials that telcagepant has been found to cause elevations in liver transaminases, there are now newer gepants such as BMS-927711 that are promising in treating acute migraine right where it begins[7,11,12,27]. This study may not be conclusive with regard to the efficacy of gepants as compared to triptans, but it joins previous studies and meta-analyses that have already proven its efficacy compared to placebo. The class of gepants now more than ever holds the great potential for effective and definitive treatment of acute migraine.

D. Recommendations for future research

Future research on the efficacy of calcitonin gene-related peptide antagonists should include more studies on the individual gepants and involve more outcomes to demonstrate efficacy, while maintaining the concept of combining the CGRP antagonists as a class. The idea of long-term efficacy should also be explored. In addition, a study that focuses not only on the efficacy, but also the safety and tolerability of the gepants as a class compared to placebo and to triptans would be most favorable. Future research with regard to the determination of any specific patient population who responds well to CGRP antagonists would also be helpful in establishing its role in the treatment of migraine.

CONCLUSION

Compared to placebo, CGRP antagonists are more efficacious in the acute treatment of migraine with regard to pain freedom and pain relief 2 hours post-dose. There is insufficient evidence to demonstrate efficacy between CGRP antagonists and triptans with regard to pain freedom and pain relief 2 hours post-dose.

Statement of Authorship

All authors have approved the final version submitted.

Author Disclosure

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