NEURAL REGENERATION RESEARCH
Volume 8, Issue 10, April 2013
www.nrronline.org

doi:10.3969/j.issn.1673-5374.2013.10.009 [http://www.nrronline.org; http://www.sjzsyj.org]
Yao G, Yu TM, Han XM, Mao XJ, Li B. Therapeutic effects and safety of olcegepant and telcagepant for migraine: a meta-analysis. Neural Regen Res. 2013;8(10):938-947.

Therapeutic effects and safety of olcegepant and telcagepant for migraine

A meta-analysis☆

Gang Yao[1, 2], Tingmin Yu[1], Ximei Han[1, 3], Xijing Mao[1], Bo Li[4]

1 *Department of Neurology, Second Hospital, Jilin University, Changchun 130041, Jilin Province, China*
2 *Department of Neurology, First Hospital, Jilin University, Changchun 130021, Jilin Province, China*
3 *Department of Neurology, Chifeng Municipal Hospital, Chifeng 024000, Inner Mongolia Autonomous Region, China*
4 *Research Room of Epidemiology and Health Statistics, School of Public Health, Jilin University, Changchun 130021, Jilin Province, China*

Abstract

OBJECTIVE: To evaluate the therapeutic effects and adverse reactions of olcegepant and telcagepant for the treatment of migraine.

DATA RETRIEVAL: We identified studies using Medline (1966-01/2012-06), PubMed (1966-01/2012-06), Scopus (1980-01/2012-06), Cochrane Central Register of Controlled Trials (1980-01/2012-06) and China National Knowledge Infrastructure (1980-01/2012-06).

SELECTION CRITERIA: The included studies were double-blind, randomized and placebo-controlled trials of olcegepant or telcagepant for the treatment of single acute migraine in patients with or without aura. Adverse reaction data were also included. Two independent investigators performed quality evaluation and data extraction using Jadad scoring. Meta-analyses were undertaken using RevMan 5.0.25 software.

MAIN OUTCOME MEASURES: Pain relief rate, pain-free rate, and incidence of adverse reactions were measured in patients 2 and 24 hours after injection of olcegepant and oral telcagepant.

RESULTS: Six randomized, controlled trials were included. Meta-analysis demonstrated that compared with placebo, the pain relief rate (odds ratio, *OR* = 5.21, 95% confidence interval, *CI*: 1.91–14.2, *P* < 0.01) and pain-free rate (*OR* = 31.11, 95% *CI*: 3.80–254.98, *P* < 0.01) significantly increased 2 hours after 2.5 mg/d olcegepant treatment. Pain relief rate and pain-free rate 2 and 24 hours after treatment with telcagepant 150 mg/d and 300 mg/d were superior to placebo (*P* < 0.01). Moreover, the remission rate of unrelenting headache was higher after 24 hours of 300 mg/d telcagepant treatment compared with 150 mg/d (*OR* = 0.78, 95% *CI*: 0.62–0.97, *P* < 0.05). The incidence of adverse reactions with olcegepant was not significantly greater than placebo (*P* = 0.28), but within 48 hours of administration of telcagepant 300 mg/d, the incidence of adverse reactions was higher than placebo (*OR* = 1.21, 95% *CI*: 1.04–1.42, *P* < 0.01). Few studies have compared the therapeutic effects of olcegepant and telcagepant.

CONCLUSION: The calcitonin-gene-related peptide receptor antagonists olcegepant and telcagepant have shown good therapeutic effects in the treatment of migraine. Moreover, the incidence of adverse reactions compares favorably with placebo, although liver transaminases may become elevated after long-term use.

Key Words

neural regeneration; evidence-based medicine; migraine; telcagepant; MK-0974; olcegepant; BIBN4096; treatment; meta-analysis; neuroregeneration

Gang Yao☆, Studying for doctorate.

Corresponding author: Tingmin Yu, M.D., Professor, Master's supervisor, Department of Neurology, Second Hospital, Jilin University, Changchun 130041, Jilin Province, China, ytm_396@163.com.

Received: 2012-10-24
Accepted: 2013-01-27
(N20120607004)

Research Highlights

(1) Phase II studies and phase III clinical randomized controlled trials of calcitonin gene-related peptide receptor antagonists olcegepant and telcagepant have been published since 2004, but there is no report that fully evaluates their therapeutic effects and adverse reactions.
(2) This paper comprehensively evaluated olcegepant and telcagepant using RevMan 5.0.25 software (provided by the Cochrane Collaboration) in accordance with the Cochrane Handbook for Systematic Reviews of Interventions.
(3) Olcegepant and telcagepant appear to be effective treatments for migraine that are well tolerated.

INTRODUCTION

Migraine is a chronic neurological disorder thought to be caused by a mixture of environmental and genetic factors that causes substantial disability. In 2004, the World Health Organization reported that 1.4% of patients with disease-induced disability have migraine[1]. The pathogenesis of migraine is complex and multifactorial, but still controversial. Recent studies have identified the main mechanisms as intracranial or extracranial vasodilatation, vasoactive peptide-induced neurogenic inflammation and impaired inhibition of central pain conduction[2]. Most hypotheses of migraine pathogenesis focus on the trigemino-vascular system as the basic pathway of pain induction and transmission.

Serotonin and calcitonin gene-related peptide have been shown to play an important role in the onset of migraine[3-4]. Triptans (serotonin receptor agonists) are a family of tryptamine-based drugs used as abortive medication in the treatment of migraines. Since the advent of sumatriptan in 1991, triptans have been the first-choice treatment for migraine. Triptans have good efficacy and tolerability, but some patients experience side effects. In particular, dizziness, paresthesia, pharyngalgia and chest discomfort can be sufficiently intrusive to oblige patients to stop taking the drugs. In addition, triptans are contraindicated in patients with cardiovascular diseases or uncontrolled hypertension, because of their potential as vasoconstrictors. Taken together, it is necessary to explore new therapeutic options for migraine.

Calcitonin gene-related peptide is a 37-amino acid peptide, which in humans exists in two forms (α-calcitonin gene-related peptide and β-calcitonin gene-related peptide [5]). It is produced in both peripheral and central neurons[6] and is a potent vasodilator[7]. The clinical application of calcitonin gene-related peptide in the treatment of migraine has been studied since the 1980s[8], as it was recognized that plasma calcitonin gene-related peptide levels increased following migraine onset and the intensity and duration of migraine were positively associated with plasma calcitonin gene-related peptide levels[9-10]. Venous administration of calcitonin gene-related peptide to patients prone to migraine can induce migraine-like headache[11]. Goadsby *et al* [12] found that calcitonin gene-related peptide levels increased in the external jugular vein during onset of migraine, but not in the ulnar vein, showing that intracranial calcitonin gene-related peptide release increased during migraine. Therefore, the calcitonin gene-related peptide receptor can be considered as a potential target for anti-migraine therapy. Calcitonin gene-related peptide receptor antagonists do not directly constrict blood vessels[13], so this paradigm theoretically provides a treatment option for patients with migraine and cardiovascular disease[14].

Indeed, in 2012, a randomized clinical trial found that a calcitonin gene-related peptide receptor antagonist was well tolerated in the treatment of migraine in patients with coronary artery disease[15]. However, preclinical studies addressing the calcitonin gene-related peptide receptor antagonists BIBN4096 (olcegepant) and MK0974 (telcagepant) had appeared at the beginning of the 21st century[16-17], followed by clinical trials from the beginning of 2004[18-24]. At present, there has not been a comprehensive evaluation of the therapeutic effects and potential adverse reactions of olcegepant and telcagepant.

This review evaluated the therapeutic effect and safety of olcegepant and telcagepant by analyzing the pain relief rate and the analgesic effects and incidence of adverse reactions of olcegepant and telcagepant for migraine in published randomized controlled clinical trials, to give guidance for their use in clinical practice and make suggestions for further investigations.

DATA SOURCES AND METHODOLOGY

Data retrieval

The key words were “olcegepant, telcagepant, BIBN4096,

MK0974, migraine, treatment". Chinese- or English-language papers were retrieved from Medline (1966-01/2012-06), PubMed (1966-01/2012-06), Scopus (1980-01/2012-06), the Cochrane Central Register of Controlled Trials (1980-01/2012-06) and China National Knowledge Infrastructure (1980-01/2012-06) databases. Three persons separately manually searched all references cited in the retrieved studies, reviews and conference proceedings.

Inclusion and exclusion criteria

Inclusion criteria: (1) double-blind, randomized, placebo-controlled trials; (2) subjects were patients with or without migraine aura, who were diagnosed using the criteria of the International Headache Society; (3) treatment of single acute migraine (studies addressing multiple migraine were included if data concerning the first onset were reported).

Interventions: we included comparative studies of therapeutic effect and adverse reaction of different doses of olcegepant and telcagepant for the treatment of migraine where other basic therapy or combined drugs were identical. The comparison of doses could be included. If a comparison of olcegepant or telcagepant was made with other drugs, we included the comparison with placebo.

Exclusion criteria: (1) non-migraine patients; (2) open trials.

Quality evaluation

Meta-analyses were performed in accordance with the guidance of the Cochrane Collaboration and the quality of reporting of meta-analyses[25-26]. Two investigators performed quality evaluation using Jadad scoring (5 points)[27]. The total score was seven points: 1–3 points, low quality; 4–7 points, high quality. Precise items contained random sequence generation, randomization concealment, application of blinding method and withdrawal (Table 1).

Data extraction

Two persons independently screened qualifying articles by reading titles and abstracts to identify whether these articles met the inclusion criteria. The same persons extracted the data, including literature references, drug dose, number of included subjects, subjects and interventions. Another two persons extracted and checked the efficiency index and the incidence rate of adverse reactions. When opinions differed, the assessment was double checked and consensus was reached by discussion.

Outcome measures

Main evaluation measures: Pain relief rate and pain-free rate 2 hours after administration; evaluation index of adverse reactions: the number of subjects who reported an adverse reaction at least once.

Secondary evaluation measures: Remission rate of unrelenting headache, disappearance rate of unrelenting pain 24 hours after administration.

Statistical analysis

The results of included studies were analyzed using RevMan 5.0.25 software provided by the Cochrane Collaboration. Data were analyzed in accordance with Cochrane Handbook for Systematic Reviews of Interventions[25]. Data were expressed as odds ratios (*OR*) and 95% confidence intervals (*CI*) to represent the therapeutic effect and adverse reactions of the calcitonin gene-related peptide receptor antagonist. The number needed to treat was also calculated[28]. Heterogeneity of trials was measured using the Chi-square test, where $X^2 > 50\%$ indicated significant heterogeneity. A combined analysis of data was conducted using a random-effect model based on the inverse variance method: $X^2 < 50\%$ indicated no significant heterogeneity. A combined quantitative analysis was undertaken using a fixed-effect model based on the Peto method[29]. Funnel plots were used to identify publication bias.

Table 1 Criteria of Jadad scoring

Random sequence generation		Randomization concealment		Application of blind method		Withdrawal	
Criteria	Jadad scoring (point)	Criteria	Jadad scoring (point)	Criteria	Jadad scoring (point)	Criteria	Jadad scoring (point)
Appropriate	2	Appropriate	2	Appropriate	2	Description	1
Unclear	1	Unclear	1	Unclear	1		
Inappropriate	0	Inappropriate	0	Inappropriate	0	No description	0
		Unused	0				

RESULTS

Retrieval results

A total of 136 papers were retrieved, all from outside China. Initially, 18 papers met the inclusion criteria. Of these, 12 papers were excluded. Two papers concerning olcegepant and one paper concerning telcagepant, whose subjects were healthy volunteers, were excluded. Five randomized trials studied telcagepant. The dose used in one trial of telcagepant (140 mg) was half that of the others (280 mg); previous results had confirmed that 280 mg telcagepant was equipotent with 300 mg[23-24]. Thus, this trial was included. Ultimately, six studies were included in the meta-analysis[18, 20-24] (Figure 1).

Results of quality evaluation

Of the six studies included[18, 20-24], three did not describe randomization concealment. The remaining three papers provided precise information about random sequence generation, randomization concealment, application of blinding method and the number of and reasons for withdrawal. The Jadad scoring of the six papers was between 4 and 7, indicating that these were high-quality papers (Table 2).

Baseline characteristics of included papers

Subjects from the six included studies[18, 20-24] were patients with or without migraine aura. Two trials compared telcagepant with zolmitriptan and rizatriptan[21-22]. One trial compared the therapeutic effects of telcagepant and ibuprofen with telcagepant and paracetamol[23]; this meta-analysis only included the data that compared telcagepant alone with placebo (Table 3).

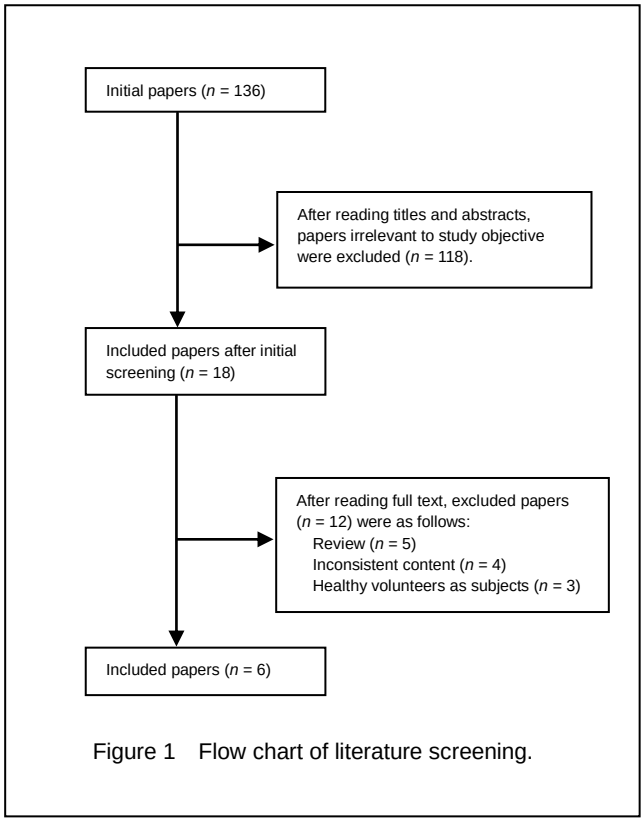

Figure 1 Flow chart of literature screening.

Meta-analysis results of evaluation of therapeutic effects

Evaluation of therapeutic effects of olcegepant

A randomized, double-blind, placebo-controlled trial[18] compared the therapeutic effects after 126 patients with migraine were administered olcegepant 2.5 mg/d or placebo.

Table 2 Quality evaluation of included papers

Paper	Random sequence generation	Score	Randomization concealment	Score	Application of blind method	Score	Withdrawal	Score	Jadad scoring
Connor *et al*, 2009[20]	Computer generation	2	Numbered container	2	Appropriate	2	Description	1	7
Ho *et al*, 2008[21]	Computer generation	2	Numbered container	2	Appropriate	2	Description	1	7
Ho *et al*, 2008[22]	Computer simulation	2	Unclear	1	Appropriate	2	Description	1	6
Olesen *et al*, 2004[18]	Telephone calling system controlled by central randomization center	2	Unclear	1	Appropriate	2	Description	1	6
Hewitt *et al*, 2011[23]	Computer generation	2	Unclear	1	Appropriate	2	Description	1	6
Ho *et al*, 2010[24]	Computer generation	2	Blister card containing drugs	2	Appropriate	2	Description	1	7

Included studies clearly described random sequence generation, application of blinding method and withdrawal. Three papers did not specifically describe the application of the blinding method.

Table 3 Baseline characteristics of included papers

Included paper	Measure		Dose (take orally; mg/d)		Treatment group/control group (*n*/*n*)	Age (year)	Gender
	Treatment group	Control group	Treatment group	Control group			
Olesen *et al*, 2004[18]	Olcegepant	Placebo	0.25, 0.5, 1, 2.5, 5, 10	Not mention	85/41	18–65	Female about 79%
Connor *et al*, 2009[20]	Telcagepant	Placebo	50, 150, 300	Corresponds to drugs	1 213/490	18	Female about 87%
Ho *et al*, 2008[21]	Telcagepant/ zolmitriptan	Placebo	Telcagepant: 150, 300; Zolmitriptan: 5	Corresponds to drugs	1 032/348	18	Female about 85%
Ho *et al*, 2008[22]	Telcagepant/ rizatriptan	Placebo	Telcagepant: 25, 50, 100, 200, 300, 400, 600; Rizatriptan: 10	Corresponds to drugs	273/147	20–65	Female about 88%
Hewitt *et al*, 2011[23]	Telcagepant+ (buprofen/ telcagepant)+ (paracetamol/ telcagepant)	Placebo	Telcagepant+buprofen: 280+400; Telcagepant+ paracetamol: 280+1 000; Telcagepant: 280	Vision matching for drugs	512/171	18	Female about 87%
Ho *et al*, Andrew, 2010[24]	Telcagepant	Placebo	140, 280	Vision matching for drugs	1 200/600	18	Female about 85%

Of the six included trials, three compared the therapeutic effect and incidence rate of adverse reactions of olcegepant or telcagepant with placebo. The remaining three studies compared the therapeutic effect and incidence rate of adverse reaction of olcegepant or telcagepant with other drugs; we only included the comparison with placebo.

Compared with placebo, the pain relief rate [*OR* = 5.21, 95% *CI*: 1.91–14.2, number needed to treat: 3[2–6], statistics of two variables, this part was the *OR* and *CI* of the number needed to treat; *P* = 0.001] and pain-free rate [*OR* = 31.11, 95% *CI*: 3.80–254.98, number needed to treat: 2[2–4]; *P* = 0.001] significantly increased 2 hours after treatment with 2.5 mg/d olcegepant (Figure 2).

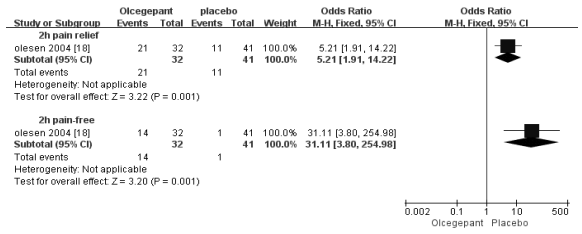

Figure 2 Comparison of therapeutic effects of olcegepant and placebo in treatment of migraine.

Evaluation of therapeutic effect of telcagepant

Comparison of telcagepant 300 mg/d with placebo: Five paperscompared the therapeutic effect of telcagepant 300 mg/d with placebo[20-24]. The results for each index as shown in Figure 1 found that I^2 < 50%, using a fixed-effect model. Compared with placebo, the pain relief rate (*OR* = 2.76, 95% *CI*: 2.39–3.20, number needed to treat: 4[3–5]; *P* < 0.01) and pain-free rate (*OR* = 2.95, 95% *CI*: 2.45–3.57, number needed to treat: 6[5–8]; *P* < 0.01) significantly increased 2 hours after 300 mg/d telcagepant treatment. Pain relief rate (*OR* = 2.88, 95% *CI*: 2.35–3.53, number needed to treat: 5[4–6]; *P* < 0.01) and pain-free rate (*OR* = 3.18, 95% *CI*: 2.55–3.95, number needed to treat: 8[7–9]; *P* < 0.01) were significantly higher than that of the placebo group 24 hours after 300 mg/d telcagepant treatment (Figure 3A).

Comparison of telcagepant 150 mg/d with placebo: three paperscompared the therapeutic effect of telcagepant 150 mg/d with placebo. Results demonstrated that compared with placebo[20-21, 24], the pain-free rate (*OR* = 2.57, 95% *CI*: 2.20–3.01, number needed to treat: 4[4–5]; *P* < 0.000 1) and pain-free rate (*OR* = 2.27, 95% *CI*: 1.83–2.82, number needed to treat: 9[7–13]; *P* < 0.000 1) at 2 hours and rate of remission of unrelenting headache (*OR* = 2.14, 95% *CI*: 1.68–2.73, number needed to treat: 7[7–13]; *P* < 0.000 1) and disappearance rate of unrelenting pain (*OR* = 2.27, 95% *CI*: 1.75–2.95, number needed to treat: 14[10–20]; *P* < 0.0001) at 24 hours were significantly higher (Figure 3B).

Comparison of therapeutic effects of telcagepant 150 mg/d and telcagepant 300 mg/d: Three paperscompared the therapeutic effects of telcagepant 150 mg/d and telcagepant 300 mg/d[20-21, 24]. The comparison of pain-free rate at 2 hours and disappearance rate of unrelenting pain at 24 hours used a random-effect model (I^2: 57%, 64%). The comparison of pain relief rate at 2 hours and remission rate of unrelenting headache at 24 hours used a fixed-effect model (I^2: 5%, 22%). Results demonstrated that the pain relief rate and pain-free rate at 2 hours and disappearance rate of unrelenting pain at 24 hours were identical after two doses.

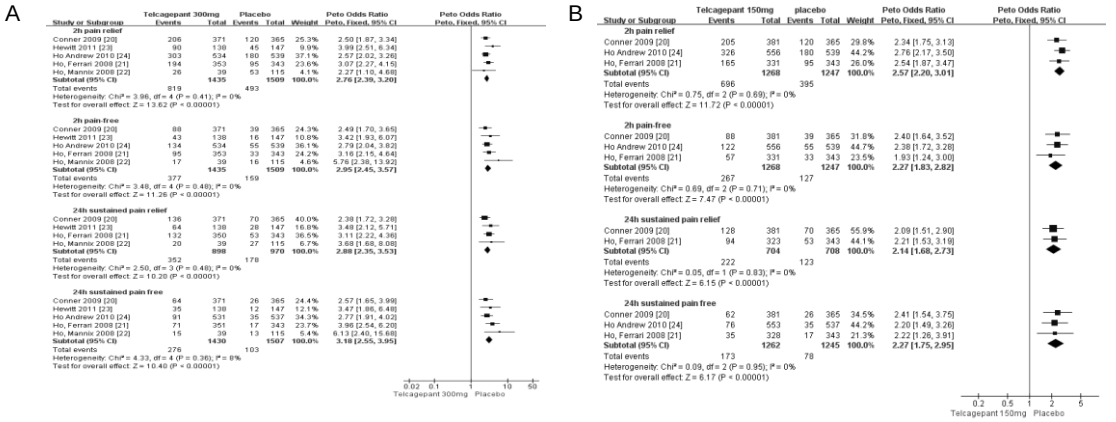

Figure 3 Pain relief rate and pain-free rate at 2 and 24 hours after oral telcagepant.

(A) Comparison of telcagepant 300 mg and placebo; (B) comparison of telcagepant 150 mg and placebo; (C) forest plot comparing telcagepant 150 mg/d and telcagepant 300 mg/d.

The pain relief rate and pain-free rate at 2 hours and disappearance rate of unrelenting pain at 24 hours were identical following the two doses of drug treatment. However, the remission rate of unrelenting headache at 24 hours was higher with telcagepant 300 mg/d than with 150 mg/d (P = 0.02).

However, the remission rate of unrelenting headache at 24 hours was higher using telcagepant 300 mg/d than using telcagepant 150 mg/d (*OR* = 0.78, 95% *CI*: 0.62–0.97, number needed to treat: 17[9–100]; *P* = 0.02) (Figure 3C).

Publication bias analysis

Five papers reported comparisons of pain relief rate and pain-free rate at 2 hours and pain-free rate at 24 hours following 300 mg/d oral telcagepant with placebo. The left and right of the funnel plot were symmetrical (Figure 4), suggesting that publication bias did not influence the results. However, fewer than five papers compared telcagepant 150 mg/d and placebo and the therapeutic effects of two doses of telcagepant.

Evaluation of adverse reactions

Adverse reactions of olcegepant

Olesen *et al* [18] compared the incidence of adverse reactions between the olcegepant 2.5 mg/d treatment group and the placebo group and found no significant difference (*OR* = 1.80, 95% *CI*: 0.61–5.28). The total incidence rate of adverse reactions was 20% in the olcegepant group, but 12% in the placebo group. Common adverse reactions included paresthesia, pain, nausea and abnormal taste and vision. Paresthesia was very common, but mild. Other adverse reactions were only found in a single case. No adverse reaction was detected on laboratory examination.

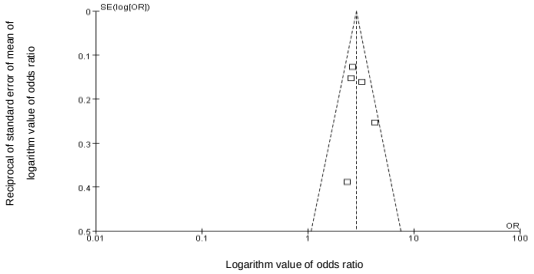

Figure 4 Funnel plot of availability of pain relief rate and pain-free rate at 2 hours and pain-free rate at 24 hours following 300 mg/d telcagepant treatment.

Adverse reactions of telcagepant

Comparison of the incidence of adverse reactions of telcagepant and placebo: in five randomized double-blind controlled trials, four[20-21, 23-24] and two[21-22] compared the incidence of adverse reactions 48 hours and 2 weeks after telcagepant treatment. The incidence of adverse reactions was higher in the telcagepant 300 mg/d group at 48 hours than that in the placebo group (*OR* = 1.21, 95% *CI*: 1.04–1.42). No significant difference was evident between the two doses when compared with placebo, or between the two doses (Figure 5).

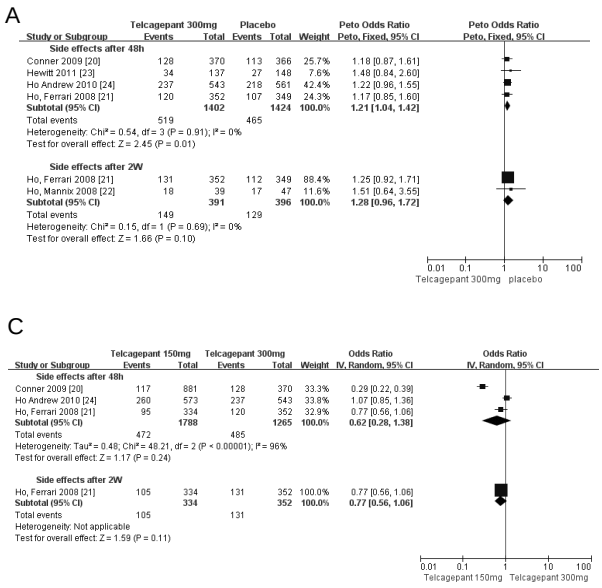

Figure 5 Evaluation of adverse reactions of telcagepant.

(A) Comparison of adverse reactions of telcagepant 300 mg and placebo; (B) comparison of adverse reactions of telcagepant 150 mg and placebo; (C) forest plot of comparison of adverse reactions of telcagepant 150 mg and telcagepant 300 mg.

Telcagepant appeared to be well tolerated. The adverse reactions were mild or moderate, including dry mouth, lethargy, dizziness, and weakness, nausea, vomiting, paresthesia and chest discomfort.

DISCUSSION

A meta-analysis contrasts and combines results from different studies and aims to analyze and evaluate a paper in the context of other publications or unpublished data[30]. Meta-analysis of studies examining the therapeutic effects and tolerability of various triptansprovided objective guidance for clinicians[31-36]. Since calcitonin gene-related peptide receptor antagonists entered clinical practice, numerous randomized controlled clinical trials have been published. Nevertheless, no meta-analysis of these trials had been undertaken. This paper sought to summarize the therapeutic effects and adverse reactions of olcegepant and telcagepant and to provide guidance for clinical therapy.

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis, this paper comprises a meta-analysis of the therapeutic effects and adverse reactions of olcegepant and telcagepant in the treatment of migraine. After retrieving reports of randomized controlled trials of olcegepant and telcagepant in Chinese- and English-language databases, ultimately six high-quality papers from outside China were included. The results show that the two drugs are effective and safe.

Olcegepant is a calcitonin gene-related peptide receptor antagonist, has an affinity and specificity for calcitonin gene-related peptide, and can effectively prevent calcitonin gene-related peptide-induced extracranial vasodilatation and migraine, although in healthy volunteers it appears not to have vasoactive effects on the cerebral circulation[13]. A previous study confirmed that the response within 10 minutes of intravenous olcegepant in patients with migraine was identical to that of triptans[24]. Another study team created a population pharmacokinetic/pharmacodynamic model describing olcegepant[37]. In a randomized, double-blind, placebo-controlled phase II trial, Olesen *et al* [18] found that olcegepant was an effective and well-tolerated treatment for acute migraine with a low incidence of adverse reactions. However, because of its low oral bioavailability, only the parenteral route can be used, limiting its use in clinical practice[38]. Since 2004, there have been no reports of clinical trials. Thus, the evaluation of the therapeutic effect and adverse reactions of olcegepant is based on the analysis of early clinical trial data.

Telcagepant acts as a calcitonin gene-related peptide receptor antagonist and has good efficacy and tolerability in the treatment of migraine. This meta-analysis included five high-quality clinical trials of telcagepant. Compared with placebo, both 150 mg/d and 300 mg/d telcagepant had a good therapeutic effect and were well tolerated. The remission rate of unrelenting headache was

significantly higher with 300 mg/d telcagepant than when 150 mg/d was used.

A phase III clinical trial compared the clinical effects of 25, 50, 100, 200, 300, 400, 600 mg telcagepant and showed lack of efficacy at lower doses (25–200 mg)[22]. However, in other studies, the therapeutic effect of telcagepant 150 mg was found to be significantly better than placebo[20-21, 24]. The difference in findings might have resulted from a small sample size in the low dose groups. Although telcagepant appears to be effective, the optimum dose should be identified by large clinical trials. In addition, two randomized controlled trials separately compared the therapeutic effects and adverse reactions of telcagepant with zolmitriptan[21] and rizatriptan[22]. The therapeutic effect of 300 mg telcagepant was greater than that of 10 mg rizatriptan, and identical to that of 5 mg zolmitriptan. There was no significant difference in the incidence of adverse reactions. In spite of this, a large randomized controlled trial is still needed to confirm this conclusion.

Regarding the evaluation of the incidence of adverse reactions, the included papers mainly selected 48 hours and 2 weeks after oral administration as time points. Frequently reported adverse reactions included dry mouth, lethargy, dizziness, weakness, nausea, vomiting, paresthesia and chest discomfort (mild or moderate). There were no severe adverse reactions. Nevertheless, Monteith *et al* [39] and Farinelli *et al* [40] reported that in a study of telcagepant 300 mg for the prophylactic treatment of migraine, of 660 subjects, liver transaminase levels became elevated in 13 participants, whose therapy was terminated. Therefore, the use of higher long-term doses of this drug could be limited.

Calcitonin gene-related peptide receptor antagonists have no vasoactive effects and provide a new therapeutic option for acute migraine[41]. The strength of the science underpinning the mechanism of action and quality of the clinical evidence led to a proliferation of further studies of olcegepant and telcagepant[42-44]. Besides telcagepant and olcegepant, we also retrieved clinical studies of MK-3207 and BI 44370 TA. MK-3207 is a potent and orally bioavailable calcitonin gene-related peptide receptor antagonist, whose bioavailability was better than MK-0974 *in vivo* and *in vitro* [45]. Only one phase II clinical trial investigated MK-3207 and found that the pain-free rate after 200 mg/d MK-3207 was superior to placebo 2 hours after administration[46]. However, MK-3207 was also found to cause elevated liver transaminases, so the study was terminated. A phase I clinical trial of BI 44370 TA has been conducted and a small phase II clinical trial reported that BI 44370 TA is effective and well tolerated[47]. These studies were not included in this meta-analysis.

Limitations of meta-analysis include unclear termination, quality differences among the original papers and publication bias. This analysis selected studies with definite termination. Two investigators independently evaluated the quality of study papers and did not find any publication bias. Nevertheless, the sample size was small, which might have influenced the results. Thus, a clinical trial with a large sample size is needed. The therapeutic effects of both telcagepant and olcegepant appear to be better than placebo, and 300 mg telcagepant was better than 150 mg. Calcitonin gene-related peptide receptor antagonists are effective and well tolerated, although high doses of drugs in the long term appear to cause derangment of hepatic function in some patients, which warrants further investigation.

Author contributions: Gang Yao participated in study authorization, data collection and analysis, statistical management and manuscript writing. Ximei Han participated in literature retrieval and evaluation, data analysis, and statistical management. Xijing Mao participated in literature retrieval and evaluation, data integration, and statistical management. Bo Li participated in statistical management and authorization. Tingmin Yu was in charge of study conception and design, manuscript authorization and study guidance. All authors approved the final version of the paper.
Conflicts of interest: None declared.
Author statements: The manuscript is original, has not been submitted to or is not under consideration by another publication, has not been previously published in any language or any form, including electronic, and contains no disclosure of confidential information or authorship/patent application disputations.

REFERENCES

[1] Leonardi M, Steiner TJ, Scher AT, et al. The global burden of migraine: measuring disability in headache disorders with WHO's Classification of Functioning, Disability and Health (ICF). J Headache Pain. 2005;6(6):429-440.
[2] Hargreaves RJ, Shepheard SL. Pathophysiology of migraine--new insights. Can J Neurol Sci. 1999;26 Suppl 3:S12-19.
[3] Ho TW, Edvinsson L, Goadsby PJ. CGRP and its receptors provide new insights into migraine pathophysiology. Nat Rev Neurol. 2010;6(10):573-582.

[4] Hamel E. Serotonin and migraine: biology and clinical implications. Cephalalgia. 2007;27(11):1293-1300.
[5] Poyner D, Marshall I. CGRP receptors: beyond the CGRP(1)-CGRP(2) subdivision? Trends Pharmacol Sci. 2001;22(5)223.
[6] Arulmani U, Maassenvandenbrink A, Villalon CM, et al. Calcitonin gene-related peptide and its role in migraine pathophysiology. Eur J Pharmacol. 2004;500(1-3): 315-330.
[7] Jansen-Olesen I, Mortensen A, Edvinsson L. Calcitonin gene-related peptide is released from capsaicin-sensitive nerve fibres and induces vasodilatation of human cerebral arteries concomitant with activation of adenylyl cyclase. Cephalalgia. 1996;16(5):310-316.
[8] Tepper SJ, Stillman MJ. Clinical and preclinical rationale for CGRP-receptor antagonists in the treatment of migraine. Headache. 2008;48(8):1259-1268.
[9] Juhasz G, Zsombok T, Modos EA, et al. NO-induced migraine attack: strong increase in plasma calcitonin gene-related peptide (CGRP) concentration and negative correlation with platelet serotonin release. Pain. 2003; 106(3):461-470.
[10] Han TH, Blanchard RL, Palcza J, et al. The dose proportionality of telcagepant after administration of single oral and intravenous doses in healthy adult subjects. Arch Drug Inf. 2010;3(4):55-62.
[11] Lassen LH, Haderslev PA, Jacobsen VB, et al. CGRP may play a causative role in migraine. Cephalalgia. 2002;22(1): 54-61.
[12] Goadsby PJ, Edvinsson L, Ekman R. Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. Ann Neurol. 1990;28(2)183-187.
[13] Petersen KA, Birk S, Lassen LH, et al. The CGRP-antagonist, BIBN4096BS does not affect cerebral or systemic haemodynamics in healthy volunteers. Cephalalgia. 2005;25(2):139-147.
[14] Dodick D, Lipton RB, Martin V, et al. Consensus statement: cardiovascular safety profile of triptans (5-HT agonists) in the acute treatment of migraine. Headache. 2004;44(5): 414-425.
[15] Ho TW, Ho AP, Chaitman BR, et al. Randomized, controlled study of telcagepant in patients with migraine and coronary artery disease. Headache. 2012;52(2): 224-235.
[16] Rudolf K, Eberlein W, Engel W, et al. Development of human calcitonin gene-related peptide (CGRP) receptor antagonists. 1. Potent and selective small molecule CGRP antagonists. 1-[N2-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidi nyl]carbonyl]-D-tyrosyl]-l-lysyl]-4-(4-pyridinyl)piperazine: the first CGRP antagonist for clinical trials in acute migraine. J Med Chem. 2005; 48(19):5921-5931.
[17] Doods H, Hallermayer G, Wu D, et al. Pharmacological profile of BIBN4096BS, the first selective small molecule CGRP antagonist. Br J Pharmacol. 2000;129(3): 420-423.
[18] Olesen J, Diener HC, Husstedt IW, et al. Calcitonin gene-related peptide receptor antagonist BIBN 4096 BS for the acute treatment of migraine. N Engl J Med. 2004; 350(11):1104-1110.
[19] Connor KM, Aurora SK, Loeys T, et al. Long-term tolerability of telcagepant for acute treatment of migraine in a randomized trial. Headache. 2011;51(1):73-84.
[20] Connor KM, Shapiro RE, Diener HC, et al. Randomized, controlled trial of telcagepant for the acute treatment of migraine. Neurology. 2009;73(12):970-977.
[21] Ho TW, Ferrari MD, Dodick DW, et al. Efficacy and tolerability of MK-0974 (telcagepant), a new oral antagonist of calcitonin gene-related peptide receptor, compared with zolmitriptan for acute migraine: a randomised, placebo-controlled, parallel-treatment trial. Lancet. 2008;372(9656):2115-2123.
[22] Ho TW, Mannix LK, Fan X, et al. Randomized controlled trial of an oral CGRP receptor antagonist, MK-0974, in acute treatment of migraine. Neurology. 2008;70(16): 1304-1312.
[23] Hewitt DJ, Martin V, Lipton RB, et al. Randomized controlled study of telcagepant plus Ibuprofen or acetaminophen in migraine. Headache. 2011;51(4): 533-543.
[24] Ho AP, Dahlof CG, Silberstein SD, et al. Randomized, controlled trial of telcagepant over four migraine attacks. Cephalalgia. 2010;30(12):1443-1457.
[25] Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009] Available from www.cochrane-handbook.org. The Cochrane Collaboration. 2009.
[26] Bero L, Rennie D. The Cochrane Collaboration. Preparing, maintaining, and disseminating systematic reviews of the effects of health care. JAMA.1995;274(24):1935-1938.
[27] Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1-12.
[28] Pan T, Wang YP, Yang JL, et al. Pancreatic duct stenting for preventing post-ercp pancreatitis: a systematic review. Zhongguo Xunzheng Yixue Zazhi. 2004;(10):693-699.
[29] Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet. 1999;354(9193): 1896-1900.
[30] Fleiss JL, Gross AJ. Meta-analysis in epidemiology, with special reference to studies of the association between exposure to environmental tobacco smoke and lung cancer: a critique. J Clin Epidemiol. 1991;44(2): 127-139.
[31] Chen LC, Ashcroft DM. Meta-analysis examining the efficacy and safety of almotriptan in the acute treatment of migraine. Headache. 2007;47(8):1169-1177.
[32] Der Simonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177-188.

[33] Ferrari MD, Loder E, McCarroll KA, et al. Meta-analysis of rizatriptan efficacy in randomized controlled clinical trials. Cephalalgia. 2001;21(2):129-136.
[34] Chen LC, Ashcroft DM. Meta-analysis of the efficacy and safety of zolmitriptan in the acute treatment of migraine. Headache. 2008;48(2):236-247.
[35] Ashcroft DM, Millson D. Naratriptan for the treatment of acute migraine: meta-analysis of randomised controlled trials. Pharmacoepidemiol Drug Saf. 2004;13(2):73-82.
[36] Ferrari MD, Roon KI, Lipton RB, et al. Oral triptans (serotonin 5-HT(1B/1D) agonists) in acute migraine treatment: a meta-analysis of 53 trials. Lancet. 2001; 358(9294):1668-1675.
[37] Troconiz IF, Wolters JM, Tillmann C, et al. Modelling the anti-migraine effects of BIBN 4096 BS: a new calcitonin gene-related peptide receptor antagonist. Clin Pharmacokinet. 2006;45(7):715-728.
[38] Iovino M, Feifel U, Yong CL, et al. Safety, tolerability and pharmacokinetics of BIBN 4096 BS, the first selective small molecule calcitonin gene-related peptide receptor antagonist, following single intravenous administration in healthy volunteers. Cephalalgia. 2004;24(8):645-656.
[39] Monteith TS, Goadsby PJ. Acute migraine therapy: new drugs and new approaches. Curr Treat Options Neurol. 2011;13(1):1-14.
[40] Farinelli I, De Filippis S, Coloprisco G, et al. Future drugs for migraine. Intern Emerg Med. 2009;4(5):367-373.
[41] Goadsby PJ. Post-triptan era for the treatment of acute migraine. Curr Pain Headache Rep. 2004;8(5)393-398.
[42] Durham PL. CGRP receptor antagonists: a new choice for acute treatment of migraine? Curr Opin Investig Drugs. 2004;5(7)731-735.
[43] Geppetti P, Capone JG, Trevisani M, et al. CGRP and migraine: neurogenic inflammation revisited. J Headache Pain. 2005;6(2)61-70.
[44] Goadsby PJ. Calcitonin gene-related peptide antagonists as treatments of migraine and other primary headaches. Drugs. 2005;65(18):2557-2567.
[45] Salvatore CA, Moore EL, Calamari A, et al. Pharmacological properties of MK-3207, a potent and orally active calcitonin gene-related peptide receptor antagonist. J Pharmacol Exp Ther. 2010;333(1):152-160.
[46] Hewitt DJ, Aurora SK, Dodick DW, et al. Randomized controlled trial of the CGRP receptor antagonist MK-3207 in the acute treatment of migraine. Cephalalgia. 2011;31(6) 712-722.
[47] Diener HC, Barbanti P, Dahlof C, et al. BI 44370 TA, an oral CGRP antagonist for the treatment of acute migraine attacks: results from a phase II study. Cephalalgia. 2011; 31(5)573-584.

(Reviewed by Wheele DW, Raye W, Wang JT, Shi TS)
(Edited by Wang J, Qiu Y, Li CH, Song LP)