Clinical Neurology and Neurosurgery 186 (2019) 105428

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

The treatment efficacy of galcanezumab for migraine: A meta-analysis of randomized controlled trials

Zhouming Ren[b], Hongmei Zhang[a,*], Ren Wang[a], Qionghui Yuan[a], Libing Pan[a], Chensong Chen[a]

[a] Department of Neurology, Ningbo Fourth Hospital, Ningbo, Zhejiang, China
[b] Department of Neurosurgery, People's Hospital of Haining, Haining, Zhejiang, 314400, China

ARTICLE INFO

Keywords:
Galcanezumab
Migraine
Randomized controlled trials
Meta-analysis

ABSTRACT

The treatment efficacy of galcanezumab for migraine remained controversial. We conducted a systematic review and meta-analysis to explore the influence of galcanezumab versus placebo on the treatment of migraine. We searched PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases through October 2018 for randomized controlled trials (RCTs) assessing the effect of galcanezumab versus placebo for patients with migraine. This meta-analysis was performed using the random-effect model.

Six RCTs were included in the meta-analysis. Overall, compared with control group for migraine patients, galcanezumab resulted in greater overall mean reduction in the number of monthly migraine headache day (MHD) ($P < 0.05$). In contrast, galcanezumab was associated with increased adverse events (risk ratio (RR) = 1.08; 95% CI = 1.01–1.15; P = 0.02), but with no significant impact on serious adverse events between two groups (RR = 2.0; 95% CI = 0.95–4.21; P = 0.07).Galcanezumab showed favorable promotion for the preventive treatment of migraine patients.

1. Introduction

Migraine was well known as a chronic, neurological disease, and ranked as 1 of the top 10 global causes of disease-related disability [1–3]. 38% of migraine patients should obtain preventive treatment, whereas only 3%–13% receive preventive therapy [4,5]. In patients with preventive treatment, high discontinuation rates were observed largely owing to a lack of efficacy and/or poor tolerability [6]. Calcitonin gene-related peptide was widely distributed in central and peripheral nervous system, and had important roles in sensory neurotransmitter, vasodilator, and mediator of neurogenic inflammation [7,8].

Calcitonin generelated peptide had strong connection with the pathophysiology of migraine, and was reported to be remarkably increased during migraine attacks [9,10]. Furthermore, migraine attacks can be triggered after infusion of calcitonin gene-related peptide to individuals with a history of migraine [8,11]. Galcanezumab was a humanized monoclonal antibody to prevent the biological activity by binding to calcitonin gene-related peptide and calcitonin gene-related peptide receptor was not blocked. Many studies provided sufficient evidence to show the potential in treating migraine [11,12].

However, the efficacy of galcanezumab versus placebo for migraine had not been well established. Recently, several studies on the topic had been published, and the results had been conflicting [12–15]. With accumulating evidence, we therefore performed a systematic review and meta-analysis of randomized controlled trials (RCTs) to compare their efficacy for migraine patients.

2. Materials and methods

Ethical approval and patient consent were not required because this was a systematic review and meta-analysis of previously published studies. The systematic review and meta-analysis were conducted and reported in adherence to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [16].

3. Search strategy and study selection

Two investigators had independently searched the following databases (inception to October 2018): PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases. The electronic search strategy was conducted using the following keywords: galcanezumab, and migraine. We also checked the reference lists of the screened full-text studies to identify other potentially eligible trials.

* Corresponding author at: Hongmei Zhang, NO 291 Donggu Road, Ningbo Fourth Hospital, Ningbo, Zhejiang, 315700, China.
E-mail addresses: 286486732@qq.com (Z. Ren), omega8281@163.com (H. Zhang), 75727646@qq.com (R. Wang), 32674582@qq.com (Q. Yuan), panlibing1111@163.com (L. Pan), ptccs@163.com (C. Chen).

https://doi.org/10.1016/j.clineuro.2019.105428
Received 6 December 2018; Received in revised form 8 June 2019; Accepted 8 July 2019
Available online 09 July 2019
0303-8467/

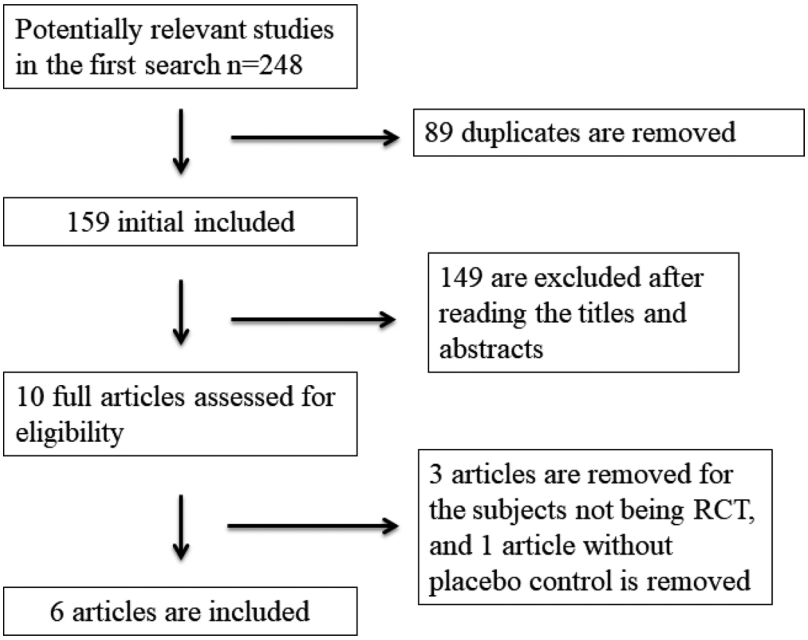

Fig. 1. Flow diagram of study searching and selection process.

The inclusive selection criteria were as follows: (i) population: patients with migraine; (ii) intervention: galcanezumab; (iii) comparison: placebo; (iv) study design: RCT.

4. Data extraction and outcome measures

We had extracted the following information: author, number of patients, age, female, body mass index, duration of migraine and detail methods in each group etc. Data had been extracted independently by two investigators, and discrepancies were resolved by consensus. We also contacted the corresponding author to obtain the data when necessary.

The primary outcomes were ≥50% response, ≥75% response, and ≥100% response (proportion of patients with ≥50%, ≥75%, and 100% reduction from baseline in monthly migraine headache day (MHD)). Secondary outcomes included overall change in MHD, change in MHD with acute medication use, migraine-specific quality of life Role function-Restrictive (MSQ RF-R), migraine disability assessment (MIDAS) total score, Patient Global Impression of Severity of Illness (PGI-S), adverse events, and serious adverse events.

5. Quality assessment in individual studies

Methodological quality of the included studies was independently evaluated using the modified Jadad scale [17]. There were 3 items for Jadad scale: randomization (0–2 points), blinding (0–2 points), dropouts and withdrawals (0–1 points). The score of Jadad Scale varied from 0 to 5 points. An article with Jadad score ≤ 2 was considered to be of low quality. If the Jadad score ≥ 3, the study was thought to be of high quality [18].

6. Statistical analysis

We estimated the standard mean difference (Std. MD) with 95% confidence interval (CI) for continuous outcomes (overall change in MHD, change in MHD with acute medication use, MSQ RF—R, MIDAS total score, and PGI-S) and risk ratios (RRs) with 95% CIs for dichotomous outcomes (≥50% response, ≥75% response, ≥100% response, adverse events, and serious adverse events). A random-effects model was used regardless of heterogeneity. Heterogeneity was reported using the I^2 statistic, and $I^2 > 50\%$ indicated significant heterogeneity [19]. Whenever significant heterogeneity was present, we searched for potential sources of heterogeneity via omitting one study in turn for the meta-analysis or performing subgroup analysis. All statistical analyses were performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

7. Results

7.1. Literature search, study characteristics and quality assessment

A detailed flowchart of the search and selection results was shown in Fig. 1. 248 potentially relevant articles were identified initially. Finally, six RCTs that met our inclusion criteria were included in the meta-analysis [12–15, 20, 21].

The baseline characteristics of the six eligible RCTs in the meta-analysis were summarized in Table 1. The six studies were published in 2018, and sample sizes ranged from 207 to 836 with a total of 3148. The intervention treatments were monthly galcanezumab 120 mg by subcutaneous injection versus placebo.

Among the six studies included here, four studies reported ≥50% response [12–14, 20], three studies reported ≥75% response [13,14,20], four studies reported ≥100% response [12–14, 20], two studies reported overall change in MHD, change in MHD with acute medication use, MSQ RF-R, MIDAS total score and PGI-S [14,20], and five studies reported adverse events and serious adverse events [12–15, 20]. Jadad scores of the six included studies varied from 3 to 5, and all six studies were considered to be high-quality ones according to quality assessment.

7.2. Primary outcomes: ≥50% response, ≥75% response, ≥100% response

These outcome data were analyzed with the random-effects model, and compared to control group for migraine, galcanezumb resulted in significantly higher ≥50% response (Std. MD = 1.54; 95% CI = 1.32–1.79; P < 0.00001) with significant heterogeneity among the studies (I^2 = 61%, heterogeneity P = 0.05) (Fig. 2), ≥75% response (Std. MD = 1.90; 95% CI = 1.59–2.27; P < 0.00001) with no heterogeneity among the studies (I^2 = 0%, heterogeneity P = 0.74)

Table 1
Characteristics of included studies.

NO.	Author	Galcanezumab group						Control group						Jada scores
		Number	Age (years)	Female (n)	Body mass index (kg/m2)	Duration of migraine (year)	Methods	Number	Age (years)	Female (n)	Body mass index (kg/m2)	Duration of migraine (year)	Methods	
1	Stauffer 2018	212	40.9 ± 11.9	181	27.8 ± 5.3	21.1 ± 13.0	galcanezumab 120 mg	433	41.3 ± 11.4	362	28.6 ± 5.5	19.9 ± 12.3	matched placebo	5
2	Skljarevski 2018 (1)	273	40.6 ± 11.9	231	–	–	galcanezumab 120 mg administered by subcutaneous injection once monthly for 3 months	137	39.5 ± 12.1	109	–	–	matched placebo	5
3	Skljarevski 2018 (2)	231	40.9 ± 11.2	197	–	19.93 ± 11.7	monthly galcanezumab 120 mg by subcutaneous injection	461	42.3 ± 11.3	393	–	21.2 ± 12.8	matched placebo	4
4	Oakes 2018	238	40	207	–	–	galcanezumab 120 mg by subcutaneous injection	120	40	106	–	–	matched placebo	3
5	Detke 2018	278	39.7 ± 11.9	237	26.4 ± 5.5	20.4 ± 12.7	galcanezumab 120 mg/month	558	41.6 ± 12.1	483	26.9 ± 5.6	21.9 ± 12.9	matched placebo	5
6	Ayer 2018	70	40.6 ± 10.9	59	–	–	galcanezumab 120 mg subcutaneous injection	137	39.5 ± 12.1	109			matched placebo	3

(Fig. 3), and ≥100% response (Std. MD = 1.98; 95% CI = 1.50–2.61; P < 0.00001) with no heterogeneity among the studies (I^2 = 0%, heterogeneity P = 0.48) (Fig. 4).

7.3. Sensitivity analysis

Significant heterogeneity was observed among the included studies for ≥50% response, but there was still significant heterogeneity when performing sensitivity analysis via omitting one study in turn.

7.4. Secondary outcomes

In comparison with control group for migraine patients, galcanezumb was associated with substantially reduced MHD (Std. MD = −6.81; 95% CI = −9.90 to −3.73; P < 0.0001; Fig. 5) and MHD with acute medication use (Std. MD = −8.19; 95% CI = −9.74 to −6.65; P < 0.00001; Fig. 6), improved MSQ RF—R (Std. MD = 6.31; 95% CI = 1.64–10.99; P = 0.008; Fig. 7), decreased MIDAS total score (Std. MD = −4.47; 95% CI = −8.51 to −0.43; P = 0.03; Fig. 8) and PGI-S (Std. MD = −2.49; 95% CI = −3.47 to −1.52; P < 0.00001; Fig. 9), but exhibited the increase in adverse events (RR = 1.08; 95% CI = 1.01–1.15; P = 0.02; Fig. 10). Serious adverse events between two groups had no statistical difference adverse events (RR = 2.0; 95% CI = 0.95–4.21; P = 0.07; Fig. 11).

8. Discussion

Migraine was a debilitating neurological disease, and resulted in a significant socioeconomic burden [22–25]. Multiple treatment options for migraine prevention had been developed, but many patients did not respond to these existing therapies [26–28]. New treatment options were needed and galcanezumab had obtained the increased focus [29,30]. One study confirmed the efficacy of galcanezumab for the preventive treatment of migraine [13]. Our meta-analysis suggested that compared to control group for migraine patients, galcanezumab had important favorable influence on the increase in ≥50% response, ≥75% response, and ≥100% response.

Patients had an average of 19.3 MHDs per month and an average MIDAS score of 65.8, suggesting very severe disability [31]. A clinically meaningful, positive change was suggested by monthly MHDs decreased by ≈5, with a difference from placebo of 2 MHDs [32]. The mean increase in functioning by 23 points on the 100-point MSQ RF—R for the galcanezumab 240-mg group was also indicative of a clinically important change [20]. The results of our meta-analysis also exhibited the obviously favorable influence on overall change in MHD, change in MHD with acute medication use, MSQ RF—R, MIDAS total score, and PGI-S after galcanezumab for the treatment of migraine. Regarding the sensitivity analysis, there was significant heterogeneity when perfuming sensitivity analysis via omitting one study in turn. This heterogeneity may be caused by different levels of severity, and treatment duration.

The safety and tolerability profiles were crucial to assess the overall therapeutic benefit of a treatment in a clinical trial [32]. Many studies had found that galcanezumab was safe and well tolerated in the episodic migraine patients, as evidenced by high rates of study completion and low rates of discontinuation due to adverse events [13–15]. The incidences of treatment-emergent adverse events were low, and the most common event was injection-site pain with the incidence of 6%–7% across galcanezumab doses. Our meta-analysis suggested galcanezumab resulted in the increase in adverse events, but showed no significant impact on serious adverse events. The most adverse reactions were mild to moderate in severity and resolved within a few days. The study comparing galcanezumab 120-mg dose and 240-mg dose reported no statistical differences of the efficacy measure for migraine patients, but may increase the incidence of injection-site related treatment emergent adverse events such as injection-site reaction, erythema,

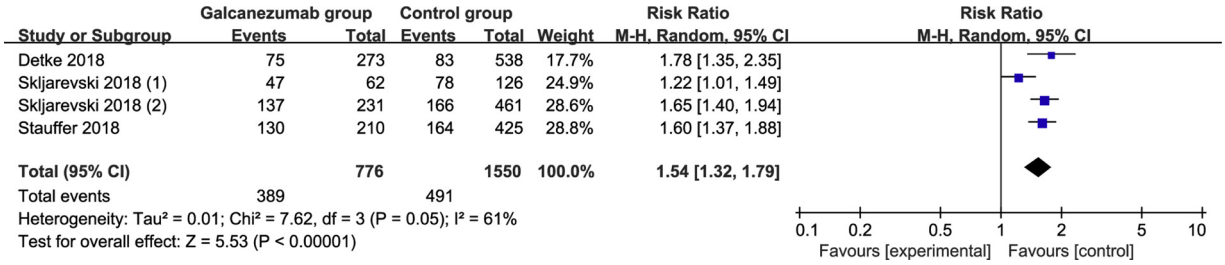

Fig. 2. Forest plot for the meta-analysis of ≥50% response.

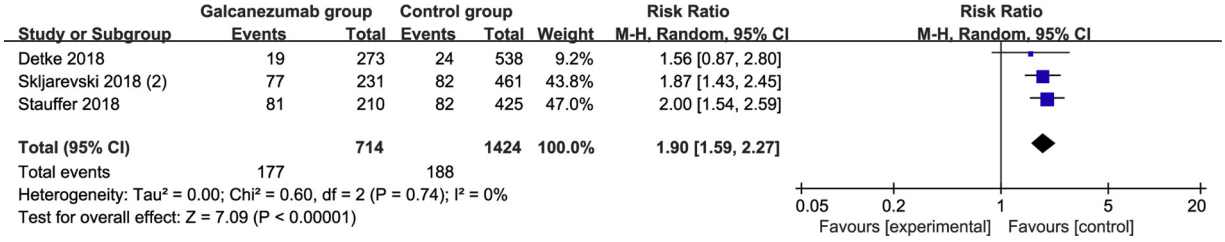

Fig. 3. Forest plot for the meta-analysis of ≥75% response.

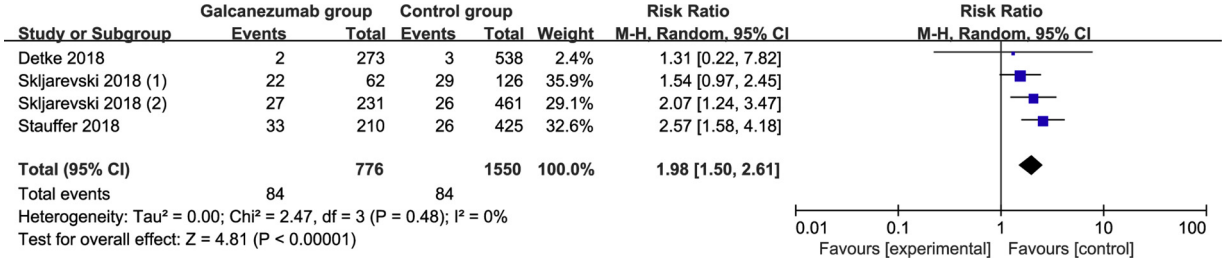

Fig. 4. Forest plot for the meta-analysis of ≥100% response.

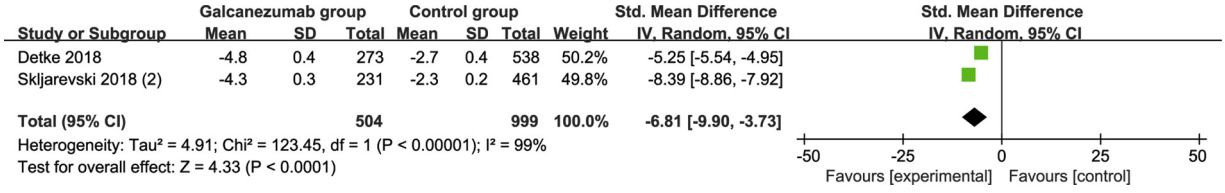

Fig. 5. Forest plot for the meta-analysis of overall change in migraine headache day (MHD).

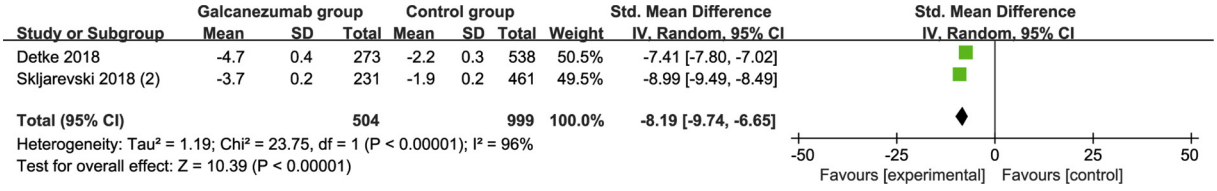

Fig. 6. Forest plot for the meta-analysis of change in migraine headache day (MHD) with acute medication use.

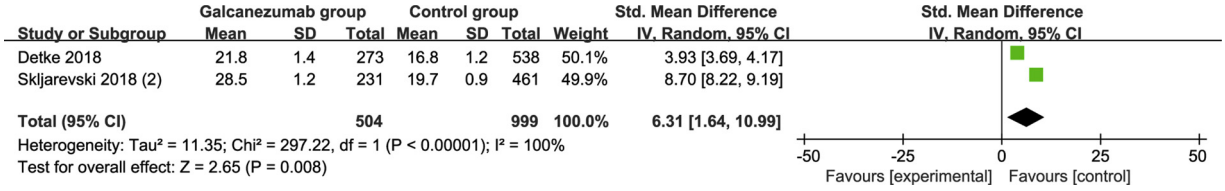

Fig. 7. Forest plot for the meta-analysis of migraine-specific quality of life Role function-Restrictive (MSQ RF-R).

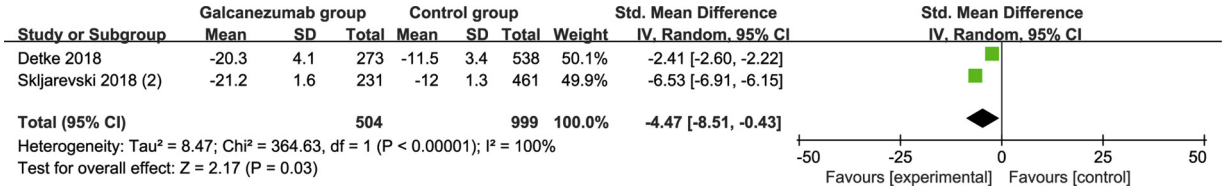

Fig. 8. Forest plot for the meta-analysis of migraine disability assessment (MIDAS) total score.

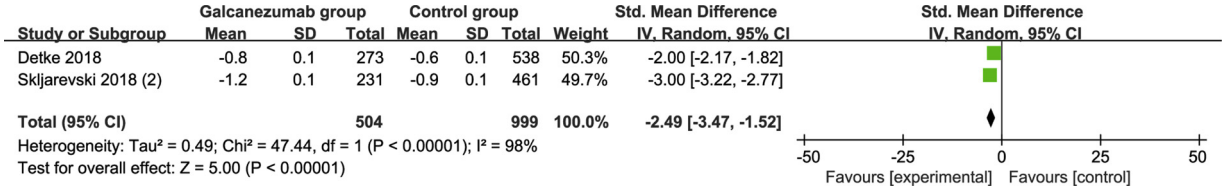

Fig. 9. Forest plot for the meta-analysis of Patient Global Impression of Severity of Illness (PGI-S).

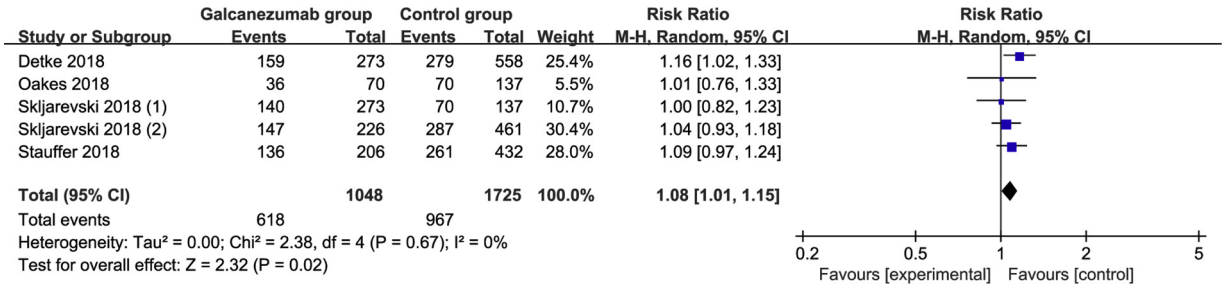

Fig. 10. Forest plot for the meta-analysis of adverse events.

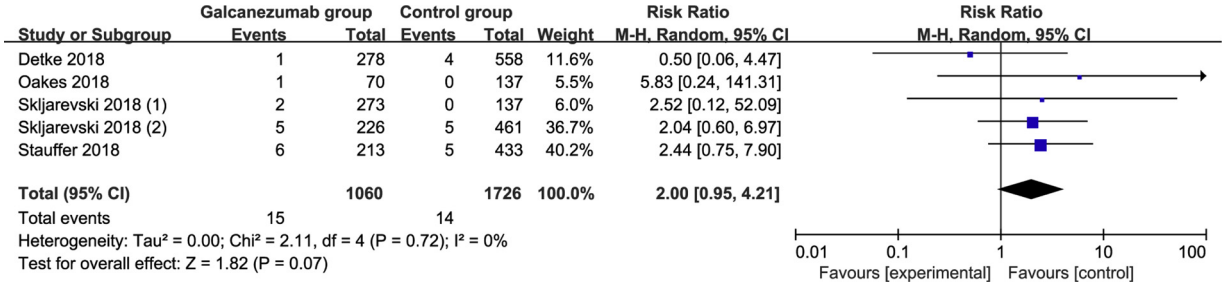

Fig. 11. Forest plot for the meta-analysis of serious adverse events.

and pruritus [20].

This meta-analysis had several potential limitations. Firstly, our analysis was based on six RCTs, and more RCTs with large sample size should be conducted to explore this issue. Next, there was significant heterogeneity which might result from different levels of migraine severity, and treatment duration. Finally, some unpublished and missing data might lead bias to the pooled effect.

9. Conclusions

Galcanezumab provided important benefits for migraine patients in terms of overall mean reduction in the number of MHD.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Conflicts of interest and source of funding

None.

Acknowledgements

None.

References

[1] Group GBDNDC, Global, regional, and national burden of neurological disorders during 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015, Lancet Neurol. 16 (2017) 877–897.
[2] E.A. MacGregor, Migraine, Ann. Intern. Med. 166 (2017) ITC49–ITC64.
[3] A. Latev, B.W. Friedman, E. Irizarry, C. Solorzano, A. Restivo, A. Chertoff, et al., A

randomized trial of a long-acting depot corticosteroid versus dexamethasone to prevent headache recurrence among patients with acute migraine who are discharged from an emergency department, Ann. Emerg. Med. (2018).
[4] R.B. Lipton, M.E. Bigal, M. Diamond, F. Freitag, M.L. Reed, W.F. Stewart, et al., Migraine prevalence, disease burden, and the need for preventive therapy, Neurology. 68 (2007) 343–349.
[5] P. Rizzoli, Preventive pharmacotherapy in migraine, Headache. 54 (2014) 364–369.
[6] A.M. Blumenfeld, L.M. Bloudek, W.J. Becker, D.C. Buse, S.F. Varon, G.A. Maglinte, et al., Patterns of use and reasons for discontinuation of prophylactic medications for episodic migraine and chronic migraine: results from the second international burden of migraine study (IBMS-II), Headache 53 (2013) 644–655.
[7] P.J. Goadsby, Bench to bedside advances in the 21st century for primary headache disorders: migraine treatments for migraine patients, Brain 139 (2016) 2571–2577.
[8] L.H. Lassen, P.A. Haderslev, V.B. Jacobsen, H.K. Iversen, B. Sperling, J. Olesen, CGRP may play a causative role in migraine, Cephalalgia 22 (2002) 54–61.
[9] P.J. Goadsby, L. Edvinsson, The trigeminovascular system and migraine: studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats, Ann. Neurol. 33 (1993) 48–56.
[10] C.M. Villalon, J. Olesen, The role of CGRP in the pathophysiology of migraine and efficacy of CGRP receptor antagonists as acute antimigraine drugs, Pharmacol. Ther. 124 (2009) 309–323.
[11] D.W. Dodick, P.J. Goadsby, E.L. Spierings, J.C. Scherer, S.P. Sweeney, D.S. Grayzel, Safety and efficacy of LY2951742, a monoclonal antibody to calcitonin gene-related peptide, for the prevention of migraine: a phase 2, randomised, double-blind, placebo-controlled study, Lancet Neurol. 13 (2014) 885–892.
[12] V. Skljarevski, T.M. Oakes, Q. Zhang, M.B. Ferguson, J. Martinez, A. Camporeale, et al., Effect of different doses of galcanezumab vs placebo for episodic migraine prevention: a randomized clinical trial, JAMA Neurol. 75 (2018) 187–193.
[13] V.L. Stauffer, D.W. Dodick, Q. Zhang, J.N. Carter, J. Ailani, R.R. Conley, Evaluation of galcanezumab for the prevention of episodic migraine: the EVOLVE-1 randomized clinical trial, JAMA Neurol. 75 (2018) 1080–1088.
[14] V. Skljarevski, M. Matharu, B.A. Millen, M.H. Ossipov, B.K. Kim, J.Y. Yang, Efficacy and safety of galcanezumab for the prevention of episodic migraine: results of the EVOLVE-2 Phase 3 randomized controlled clinical trial, Cephalalgia 38 (2018) 1442–1454.
[15] T.M.M. Oakes, V. Skljarevski, Q. Zhang, W. Kielbasa, M.E. Hodsdon, H.C. Detke, et al., Safety of galcanezumab in patients with episodic migraine: a randomized placebo-controlled dose-ranging Phase 2b study, Cephalalgia 38 (2018) 1015–1025.
[16] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, P. Group, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, J. Clin. Epidemiol. 62 (2009) 1006–1012.
[17] A.R. Jadad, R.A. Moore, D. Carroll, C. Jenkinson, D.J.M. Reynolds, D.J. Gavaghan, et al., Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control. Clin. Trials 17 (1996) 1–12.
[18] L.L. Kjaergard, J. Villumsen, C. Gluud, Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses, Ann. Intern. Med. 135 (2001) 982–989.
[19] J.P. Higgins, S.G. Thompson, Quantifying heterogeneity in a meta-analysis, Stat. Med. 21 (2002) 1539–1558.
[20] H.C. Detke, P.J. Goadsby, S. Wang, D.I. Friedman, K.J. Selzler, S.K. Aurora, Galcanezumab in chronic migraine: the randomized, double-blind, placebo-controlled REGAIN study, Neurology (2018).
[21] D.W. Ayer, V. Skljarevski, J.H. Ford, A.W. Nyhuis, R.B. Lipton, S.K. Aurora, Measures of functioning in patients with episodic migraine: findings from a double-blind, randomized, placebo-controlled phase 2b trial with galcanezumab, Headache 58 (2018) 1225–1235.
[22] T. Vos, A.D. Flaxman, M. Naghavi, R. Lozano, C. Michaud, M. Ezzati, et al., Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010, Lancet 380 (2012) 2163–2196.
[23] M. Leonardi, T.J. Steiner, A.T. Scher, R.B. Lipton, The global burden of migraine: measuring disability in headache disorders with WHO's Classification of Functioning, Disability and Health (ICF), J. Headache Pain 6 (2005) 429–440.
[24] D.E. Chou, M. Shnayderman Yugrakh, D. Winegarner, V. Rowe, D. Kuruvilla, J. Schoenen, Acute migraine therapy with external trigeminal neurostimulation (ACME): a randomized controlled trial, Cephalalgia (2018) 333102418811573.
[25] T.J. Schwedt, J. Peplinski, P. Garcia-Filion, V. Berisha, Altered speech with migraine attacks: A prospective, longitudinal study of episodic migraine without aura, Cephalalgia (2018) 333102418815505.
[26] E.W. Loder, P. Rizzoli, Tolerance and loss of beneficial effect during migraine prophylaxis: clinical considerations, Headache 51 (2011) 1336–1345.
[27] P.J. Goadsby, T. Sprenger, Current practice and future directions in the prevention and acute management of migraine, Lancet Neurol. 9 (2010) 285–298.
[28] G. Coppola, C. Di Lorenzo, M. Serrao, V. Parisi, J. Schoenen, F. Pierelli, Pathophysiological targets for non-pharmacological treatment of migraine, Cephalalgia 36 (2016) 1103–1111.
[29] A.R. Tso, P.J. Goadsby, Anti-CGRP monoclonal antibodies: the next era of migraine prevention? Curr. Treat. Options Neurol. 19 (2017) 27.
[30] J.M. Woolley, M.M. Bonafede, B.A. Maiese, R.A. Lenz, Migraine prophylaxis and acute treatment patterns among commercially insured patients in the United States, Headache 57 (2017) 1399–1408.
[31] A.M. Blumenfeld, S.F. Varon, T.K. Wilcox, D.C. Buse, A.K. Kawata, A. Manack, et al., Disability, HRQoL and resource use among chronic and episodic migraineurs: results from the International Burden of Migraine Study (IBMS), Cephalalgia 31 (2011) 301–315.
[32] D.W. Dodick, C.C. Turkel, R.E. DeGryse, H.C. Diener, R.B. Lipton, S.K. Aurora, et al., Assessing clinically meaningful treatment effects in controlled trials: chronic migraine as an example, J. Pain 16 (2015) 164–175.