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Increased infection risk in patients on preventive CGRP-targeting therapies– a meta-analysis and clinical effect assessment

Marcin Straburzyński[1*], Daria Kopyt[2], Karol Marschollek[3], Bartłomiej Błaszczyk[3], Ewa Kuca-Warnawin[4], Weronika Kurowska[4], Błażej Misiak[5], Kuan-Po Peng[6], Marta Waliszewska-Prosół[3] and Arne May[6]

Abstract

Background Calcitonin gene related peptide (CGRP) pathway targeting therapies have proven efficacy, safety and tolerability. However, CGRP is also involved in immune responses, and reports of an increased risk of infection have emerged. This meta-analysis aims to verify whether CGRP-targeting therapies show evidence of increasing infection risk.

Methods A systematic review was conducted according to PRISMA-Harms guidelines. A PubMed and Embase search result selection and extraction was performed. Risk of bias, sensitivity analysis, and fixed/random effects network meta-analyses were conducted for incidence of infectious adverse events in the studied populations with subsequent effect size assessment. An additional infectious serious adverse event search was performed in double-blind and open-label studies.

Results The search and selection process yielded 37 randomized placebo-controlled trials. 22,518 patients (77.3% women) treated with erenumab, fremanezumab, galcanezumab, eptinezumab, atogepant and rimegepant participated in these studies. Preventive CGRP-targeting therapies appear to increase the infection relative risk (RR = 1.08 [1.01; 1.14], $p = 0.016$, Number Needed to Harm [NNH] = 287). However, in individual analyses only galcanezumab and eptinezumab showed an increase in risk of infections: galcanezumab at clinically used doses (RR 1.13 [1.02; 1.25], $p = 0.024$, NNH = 77); eptinezumab at higher doses (RR 1.23 [1.04; 1.45], $p = 0.015$, NNH = 24). Fremanezumab was associated with fewest infectious SAEs ($n = 3$ in 3 studies), while erenumab showed the highest incidence of these events ($n = 36$ in 11 studies).

Conclusions CGRP has multiple and often potentially opposing effects on the immune system. In effect, preventive CGRP pathway antagonists (especially eptinezumab and galcanezumab) possibly only mildly increase the risk of infections. However, it is unlikely to affect most migraine patients considering relatively high NNH, low effect size and few infectious SAEs reported so far. The result of CGRP-targeting therapies potentially depends on the type of pathogen and patient's immune status. Consequently, in immunocompromised patients or at public health levels the increased infection risk may have more pronounced effect.

*Correspondence:
Marcin Straburzyński
marcin.straburzynski@uwm.edu.pl

Full list of author information is available at the end of the article

Keywords Erenumab, Fremanezumab, Galcanezumab, Eptinezumab, Atogepant, Rimegepant, Migraine, Infection, CGRP

Background

Calcitonin gene related peptide (CGRP) pathway targeting therapies are becoming a staple in migraine management [1, 2]. It is a consequence of their confirmed efficacy in migraine prevention [3] and (in the case of some gepants) acute treatment [4]. Moreover, favourable tolerability and safety have been reported [5]. However, reports have also emerged of an increased infection risk for respiratory tract infections in the case of erenumab [6] and galcanezumab [7] as well as urinary tract infections for atogepant [8] and in some cases rimegepant [9]. Should these reports be confirmed, a significant impact on individual and public health could be expected considering the high prevalence of migraine [10] which may affect also people with immune system disorders [11].

CGRP plays various roles in humans that are not limited to headache aetiopathogenesis, but are also involved in immune response [12, 13]. CGRP potentially takes part in response to viral [14], bacterial [15], fungal [16] infections and parasitic infestations [17]. Therefore, investigating the association between the CGRP blockade and the risk of infection is of significant clinical importance. Despite that, infection rates have not been assessed in a systematic manner in people treated with CGRP-targeting medications. Consequently, it is unclear whether the increased risk of infections mentioned in the previous paragraph is a class effect in response to CGRP pathway blockade.

The purpose of this meta-analysis is to identify whether CGRP-targeting therapies show evidence of increasing infection. We hypothesized that CGRP-targeting medications may cause infections and that this effect may vary depending on the medication dose or infection type.

Methods

Eligibility criteria

The meta-analysis was performed according to the 'PRISMA-Harms' reporting guidelines [18]. The protocol was recorded in the international prospective register of systematic reviews (PROSPERO CRD42024588786). The following inclusion criteria were followed:

- unlimited publication dates prior to database search.
- full text available in English language.
- trials in adult patients treated with registered CGRP-targeting monoclonal antibodies or CGRP-receptor antagonists for at least 12 weeks.
- at least one infectious adverse event in a published manuscript and/or its supplementary materials.
- studies considered for meta-analysis: randomised, double-blind, placebo-controlled, registered trials.

The selected studies were cross-referenced with the clinicaltrials.gov registry for AEs, as different approaches to AE reporting thresholds may have been used in these sources. The studied populations were not restricted in respect to diagnosis (i.e. disorders other than migraine were not excluded). Trials in children and adolescents were excluded as currently no CGRP-targeting medication is registered for people under the age of 18. Studies on acute treatment were excluded due to the fact that not all their participants took gepants daily or every other day. Unregistered therapies (i.e. 1st generation gepants) were excluded due to unacceptable safety profiles and limited generalizability to everyday practice. Active comparator trials without placebo group were excluded. Studies that did not provide data on the number of AEs or the number of patients who experienced AEs were also excluded. Duplicate records and post-hoc analyses were excluded unless they presented new data on infectious AEs.

Database search and data extraction

The database search was performed at one time-point (17 Sep. 2024) in PubMed and Embase. The search phrase was defined as: ((erenumab) AND (Placebo)) OR ((erenumab) AND (real world)) OR ((erenumab) AND (open-label)) OR ((AMG 334) AND (Placebo)) OR ((AMG 334) AND (real world)) OR ((AMG 334) AND (open-label)) OR ((fremanezumab) AND (Placebo)) OR ((fremanezumab) AND (real world)) OR ((fremanezumab) AND (open-label)) OR ((TEV-48125) AND (Placebo)) OR ((TEV-48125) AND (real world)) OR ((TEV-48125) AND (open-label)) OR ((LBR-101) AND (Placebo)) OR ((LBR-101) AND (real world)) OR ((LBR-101) AND (open-label)) OR ((galcanezumab) AND (Placebo)) OR ((galcanezumab) AND (real world)) OR ((galcanezumab) AND (open-label)) OR ((LY2951742) AND (Placebo)) OR ((LY2951742) AND (real world)) OR ((LY2951742) AND (open-label)) OR ((eptinezumab) AND (Placebo)) OR ((eptinezumab) AND (real world)) OR ((eptinezumab) AND (open-label)) OR ((ALD403) AND (Placebo)) OR ((ALD403) AND (real world)) OR ((ALD403) AND (open-label)) OR ((atogepant) AND (Placebo)) OR ((atogepant) AND (real world)) OR ((atogepant) AND (open-label)) OR ((AGN-241689) AND (Placebo)) OR ((AGN-241689) AND (real world)) OR ((AGN-241689) AND (open-label)) OR ((rimegepant) AND (Placebo)) OR ((rimegepant) AND (real world)) OR ((rimegepant)

AND (open-label)) OR ((BMS-927711) AND (Placebo)) OR ((BMS-927711) AND (real world)) OR ((BMS-927711) AND (open-label)].

Two authors (DK and KM) independently assessed the results obtained in the database search. The first step involved title and abstract (PubMed and Embase) assessment for eligibility according to inclusion and exclusion criteria. In the second step, the manuscripts of publications selected in the first step were analysed. Any discrepancies between the authors were resolved by the third author (MS) separately, after the first and second step analysis.

Data extraction from selected manuscripts or their supplements and clinicaltrials.gov records was performed separately by DK and KM. If discrepancies were found between sources describing the same study (e.g. manuscript and clinicaltrials.gov database) then the higher number of AEs was included in the meta-analysis. This was due to the fact that manuscripts often underreport AEs if a given threshold of participants is not reached, whereas trial registries in some situations may present more data. The AEs were classified to one of the categories according to Table 1. When an AE was described with a specific aetiology different from that proposed in Table 1, it was classified accordingly (e.g. COVID-19 pneumonia was classified as viral rather than bacterial). Data excluded from the extraction involved inflammatory disorders of predominantly non-infectious aetiology or infections secondary to another event. Other excluded AEs involved: chronic sinusitis (unless during exacerbation), chronic obstructive pulmonary disease (unless during exacerbation), cholecystitis, appendicitis, gastritis (unless classified as infective), vector borne diseases (incl. Lyme disease and Denga), neuritis, uveitis and gingivitis (unless classified as infective).

Table 1 Adverse events to be extracted from included studies. COVID-19– Coronavirus disease 2019

Adverse event (synonym)	Predominant aetiology
Upper respiratory tract infection	Viral
Nasopharyngitis (rhinitis, pharyngitis, tonsillitis)	
Sinusitis (rhinosinusitis)	
Otitis media	
Herpes	
Laryngitis	
Tracheitis	
Bronchitis	
COVID-19	
Gastroenterocolitis	
Meningitis	
Other viral	
Otitis externa	Bacterial
Mastoiditis	
Exacerbation of chronic obstructive pulmonary disease	
Pneumonia	
Tuberculosis	
Urinary tract infection (cystitis)	
Pyelonephritis	
Vagnitis (vulvovaginitis)	
Sepsis (urosepsis)	
Diverticulitis	
Cellulitis	
Folliculitis	
Hordeolum (chalazion)	
Abscess	
Other bacterial	
Unclassified or other	Other

Apart from data for the meta-analysis, a separate extraction of infectious serious AEs (SAEs) was performed in randomized placebo-controlled and open-label (OL) trials, as well as published real-world evidence (RWE). In this case, only trials that reported at least one infectious SAE were included. Search and selection strategies were similar to those described above, but with adjustments regarding study type. Data from the entire selection and extraction process is available in the publicly available repository [19].

Statistical analysis and quality assessment

It was conducted using both fixed-effect and random-effect models. The statistical heterogeneity was assessed using Cochran's Q test, I^2 statistic and Pearson χ^2 tests. The Biggerstaff and Jackson method was applied to determine the statistical significance of heterogeneity. Baujat plots were employed to identify studies contributing to the heterogeneity and influencing the overall result of the meta-analysis. If the heterogeneity tests indicated a low risk of heterogeneity ($p > 0.001$, $I^2 < 25\%$), the fixed-effect model was applied for the meta-analysis. The Pearson χ^2 test was used for the analysis of contingency tables to assess statistically significant differences between the expected (placebo) frequencies and the observed frequencies. When significant differences ($p < 0.05$) were found, the treatment-related relative risk (RR) of infection was calculated. In the case of contingency Table (2×2), the following classification of effect size was adopted: small ($1.0 < RR < 1.5$), medium ($1.5 \leq RR < 2.5$) and large ($RR \geq 2.5$). Furthermore, Number Needed to Harm (NNH) was calculated to assess the risk of a harmful side effects as 1/RD. Risk Difference (RD) was calculated as: RD = EER– CER. EER is the percentage of participants in the experimental group who experienced an adverse effect (infection), and CER is the percentage of participants in the control group who experienced the same adverse effect.

RR estimations were performed in subgroups depending on medication and dose ('any dose', 'any clinically

registered dose' and 'high dose'). The doses were considered high when they were equal to or above the highest registered dose (e.g. erenumab ≥ 140 mg monthly, fremanezumab ≥ 675 mg per 3 months, galcanezumab ≥ 240 mg monthly, eptinezumab ≥ 300 mg quarterly, atogepant ≥ 60 mg per day, rimegepant > 75 mg every second day). Alternatively, a dose associated with temporal exposition to higher medication doses (e.g. quarterly fremanezumab 675 mg). Meta-analysis was also performed for pooled data for all included particles at clinically registered dose and high doses. In case of infections the data was pooled for overall infections, viral infections, coronavirus disease 2019 (COVID-19), bacterial infections UTIs for each subanalysis. COVID-19 was selected due to its potentially lower risk of reporting bias compared to other respiratory tract infections, especially during the first years of pandemic. RR estimates were calculated for data pooled across all indications. Age and sex were chosen as they are associated with increased risk of some infections [20, 21]. The publication date was chosen as potential moderator to exclude risk related to unidentified drift in study methods.

The Cochrane tool for assessing risk of bias in randomised trials version 2 (RoB 2) was used. Publication bias was analysed in the symmetry of funnel plots, the 'trim-and-fill' method and the Egger's test. The I-squared (I^2) statistic was used to describe the percentage of the total variance in study results that is attributable to heterogeneity rather than chance. Although not a formal statistical test, I^2 helps in assessing the degree of heterogeneity (e.g., low, moderate, high). Studies with high bias risk were to be excluded from the analysis. A random-effect meta-regression of the extracted data concerning sex, age, and publication date was performed to estimate the effect of each moderator on the final outcome variable. Galbraith plots were used to assess the consistency of study results and identify outliers. The effect size of age, sex and publication date was calculated as Hedges' g with corresponding 95% confidence intervals (95% CI).

Results

PubMed and Embase databases search yielded 1138 results in total. The selection process has been presented in Fig. 1. Altogether, 37 trials eligible for data extraction and meta-analysis were found. Studies included in the meta-analysis are listed in Table 2. These trials evaluated two gepants and four monoclonal antibodies currently registered for migraine prevention. A total of 22 518 participants (77.3% women) were randomised in the included trials. Dosing schemes included registered and unregistered regimens for different forms of migraine or chronic cluster headache. Risk of bias of individual studies was low (Supplement 8), although lack of systematic evaluation of infectious AEs (e.g. via validated questionnaires) and reporting thresholds may have led to missed infections. However, no signs of infection reporting bias was identified.

Erenumab

The meta-analysis included 10 studies with 5704 participants aged 41.9 (SD = 11.8). The details of each analysis have been presented in Supplement 1. The studies had low heterogeneity ($Q = 7.59$, $df = 9$, $p = 0.576$, $I^2 = 0.00\%$) and their publication bias was also low in funnel plot and Egger's tests (t = -0.942, $df = 8$, $p = 0.374$). Additionally, the 'trim-and-fil test' did not identify biased trials. L'Abbe and Galbraith diagram analysis showed that particular study results followed the combined effect. Sensitivity analysis did not show that the exclusion of one study from the analysis led to a significant RR change.

Erenumab has not been shown to increase the risk of viral, bacterial, UTI and overall infection risk (Table 3). These results were consistent across 'high', 'registered/clinical' (Fig. 2) or 'any' dosing schemes. There was only one study assessing COVID-19 [31], so in that case a meta-analysis could not be performed. In this trial erenumab significantly increased the risk of COVID-19 infection. In this case the RR of COVID-19 was 2.07 [1.18, 3.61, $p = 0.008$, power of the test being calculated post-hoc was 1 - $\beta = 0.84$]. In other words, erenumab has a medium effect on COVID-19 infection risk. None of the four moderating variables included in the meta-regression (gender, age, sample size, and year of publication) had a significant impact on the overall effect of the meta-analysis.

Fremanezumab

The meta-analysis included 7 studies with 4327 participants aged 42.7 years (SD = 11.4). The details of each analysis have been presented in Supplement 2. The studies had low heterogeneity ($Q = 1.62$, $df = 6$, $p = 0.951$, $I^2 = 0.00\%$) and their publication bias was also low in funnel plot and Egger's tests ($t = 0.411$, $df = 5$, $p = 0.698$). Moreover, the 'trim-and-fil test' did not identify biased trials. L'Abbe and Galbraith diagram analysis showed that particular study results followed the combined effect. Sensitivity analysis did not show that the exclusion of one study from the analysis led to a significant RR change.

Fremanezumab has not been shown to increase the risk of viral, bacterial, UTI and overall infection risk (Table 4). The results were consistent across 'high', 'registered/clinical' (Fig. 3) or 'any' dosing schemes. None of the four moderating variables included in the meta-regression had a significant impact on the overall effect of the meta-analysis.

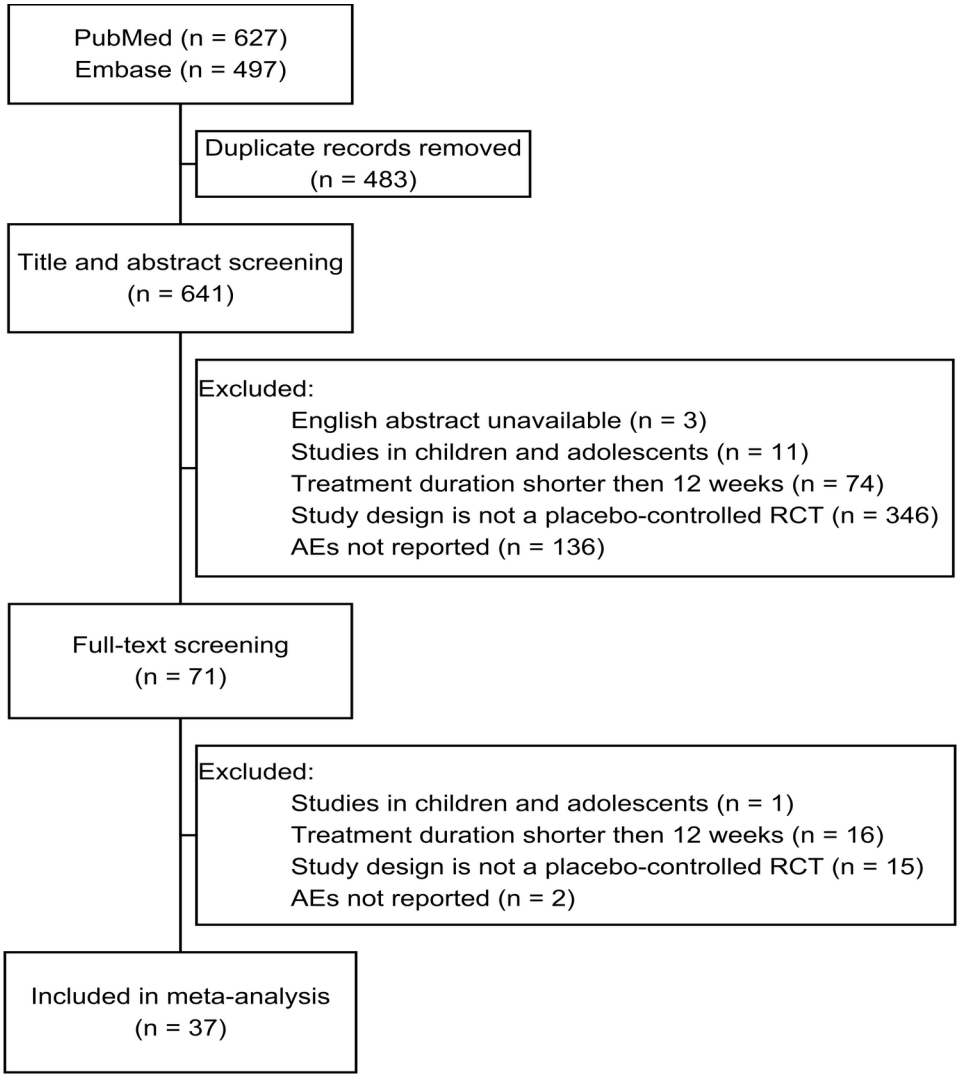

Fig. 1 Flow chart of study selection

Galcanezumab

The meta-analysis included 9 studies with 5191 participants aged 41.8 years (SD = 11.3). The details of each analysis have been presented in Supplement 3. The studies had low heterogeneity (Q = 6.94, df = 8, $p = 0.543$, $I^2 = 0.00\%$) and their publication bias was also low in funnel plot and Egger's tests (t = 1.543, df = 7, $p = 0.167$). Furthermore, the 'trim-and-fil test' did not identify biased trials. L'Abbe and Galbraith diagram analysis showed that results followed the combined effect. Sensitivity analysis did not show that the exclusion of one study from the analysis led to a significant RR change. However, one exception was subanalysis of UTIs where excluding one publication (RCT5 [43]) significantly affected the result of the meta-analysis. The relative risk of UTIs after excluding this study will be RR = 1.74 [(1.00; 3.00), $p = 0.049$], which indicates result bordering on insignificance.

Galcanezumab increased the overall risk of any or viral infections at clinical doses (Table 5, Fig. 4). The number needed to harm (NNH) for any infection was 77 (E1 = 328, E0 = 1055, C1 = 517, C0 = 1790). In this case the RR of infection was 1.13 [1.00, 1.28, $p = 0.024$, power of the test calculated post-hoc was 1 - β = 0.81]. In other words, galcanezumab has a small effect on infection risk. No increase in infection risk was found for bacterial infections, COVID-19 or UTIs. The results were not significant for high or 'any dose's used. In patients receiving high doses of galcanezumab female sex was associated with lower risk of infections (b = -0.010, Z = -2.003, $p = 0.045$). None of the other three moderating variables included in the meta-regression had a significant impact on the overall effect of the meta-analysis.

Table 2 Table 2 studies included in the meta-analysis

Active substance		Study registration number	Maximal single doses (mg)	Participants randomised (*n*)	Diagnosis
Erenumab	Reuter et al. 2018 [22]	NCT03096834	140	243	RM
	Sun et al. 2016 [23]	NCT01952574	7, 21, 70	472	EM
	Tepper et al. 2017 [24]	NCT02066415	70, 140	660	CM
	Goadsby 2017 et al. [25]	NCT02456740	70, 140	952	EM
	Sakai et al. 2019 [26]	NCT02630459	28, 70, 140	474	EM
	Takeshima et al. 2021 [27]	NCT03812224	70	261	RM
	Dodick et al. 2018 [28]	NCT02483585	70	572	EM
	Wang et al. 2021 [29]	NCT03333109	70, 140	894	EM
	Yu et al. 2022 [30]	NCT03867201	70	557	CM
	Tepper et al. 2024 [31]	NCT03971071	70, 140	619	CM + MO
Fremanezumab	Dodick et al. 2018 [32]	NCT02629861	225, 675	875	EM
	Ferrari et al. 2019 [33]	NCT03308968	225, 675	838	EM, CM
	Bigal et al. 2015 [34]	NCT02021773	225, 675, 900	263	CM
	Silberstein et al. 2017 [35]	NCT02621931	225, 675	1130	CM
	Sakai et al. 2021 [36]	NCT03303079	225, 675	569	CM
	Bigal et al. 2015 (2) [37]	NCT02025556	225, 675	296	HFEM
	Sakai et al. 2021 (2) [38]	NCT03303092	225, 675	356	EM
Galcanezumab	Skljarevski et al. 2018 [39]	NCT02163993	5, 50, 12, 300	410	EM
	Stauffer et al. 2018 [40]	NCT02614183	120, 240	858	EM
	Dodick et al. 2014 [41]	NCT01625988	150	217	Migraine
	Mulleners et al. 2020 [42]	NCT03559257	120	462	RM
	Skljarevski et al. 2018 (2) [43]	NCT02614196	120, 240	915	EM
	Dodick et al. 2020 [44]	NCT02438826	300	237	CCH
	Hu et al. 2022 [45]	NCT03963232	120, 240	520	EM
	Detke et al. 2018 [46]	NCT02614261	120, 240	1113	CM
	Sakai et al. 2020 [47]	NCT02959177	120, 240	459	EM
Eptinezumab	Ashina et al. 2022 [48]	NCT04418765	100, 300	891	RM
	Dodick et al. 2014 (2) [49]	NCT01772524	1000	163	HFEM
	Yu et al. 2023 [50]	NCT04772742	100	193	CM + MO
	Dodick et al. 2019 [51]	NCT02275117	10, 30, 100, 300	617	CM
	Ashina et al. 2020 [52]	NCT02559895	30, 100, 300	888	EM
	Lipton et al. 2020 [53]	NCT02974153	100, 300	1072	CM
Atogepant	Ailani et al. 2021 [54]	NCT03777059	10, 30, 60	902	EM
	Pozo-Rosich et al. 2023 [55]	NCT03855137	30, 60	773	CM
	Goadsby et al. 2020 [56]	NCT02848326	10, 30, 60	825	EM
	Tassorelli et al., 2024 [57]	NCT04740827	60	313	RM
Rimegepant	Croop et al. 2021 [58]	NCT03732638	75	741	Migraine

EM– episodic migraine, CM– chronic migraine, RM– resistant migraine, MOH– medication overuse, CCH– chronic cluster headache, HFEM– high frequency episodic migraine

Table 3 Dose and infection-type dependent risk of infection in patients treated with erenumab vs. Placebo

Erenumab dose	Statistics	Infection				
		Any	Viral	Bacterial	COVID-19*	UTI
Any	*p*- value	0.753	0.464	0.921	**0.008**	0.561
	RR	1.04	1.04	1.03	**2.07**	0.77
Clinical	*p*-value	0.397	0.447	0.615	**0.008**	0.720
	RR	1.05	1.05	1.15	**2.07**	0.88
High	*p*-value	0.140	0.300	0.597	0.005	0.827
	RR	1.13	1.12	1.19	**2.35**	0.92

COVID-19 - Coronavirus disease 2019; *Only one study assessed COVID-19 frequency, so the results regarding this infection represent risk reported

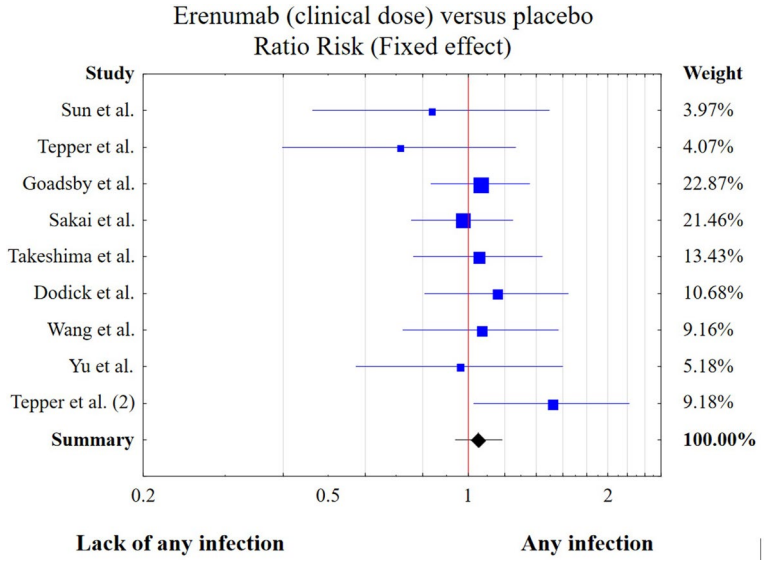

Fig. 2 Risk of any infection in patients treated with clinical doses of erenumab vs. placebo

Table 4 Dose and infection-type dependent risk of infection in patients treated with fremanezumab vs. placebo

Fremanezumab dose	Statistics	Infection				
		Any	Viral	Bacterial	COVID-19	Urinary
Any	*p*- value	0.900	0.894	0.960	-	0.812
	RR	1.01	0.99	1.01		1.08
Clinical	*p*-value	0.457	0.429	0.625	-	0.646
	RR	1.08	1.07	1.15		1.18
High	*p*- value	0.855	0.602	0.650	-	0.345
	RR	0.99	0.95	1.12		1.37

COVID-19 - Coronavirus disease 2019; UTI– urinary tract infection; RR– risk ratio

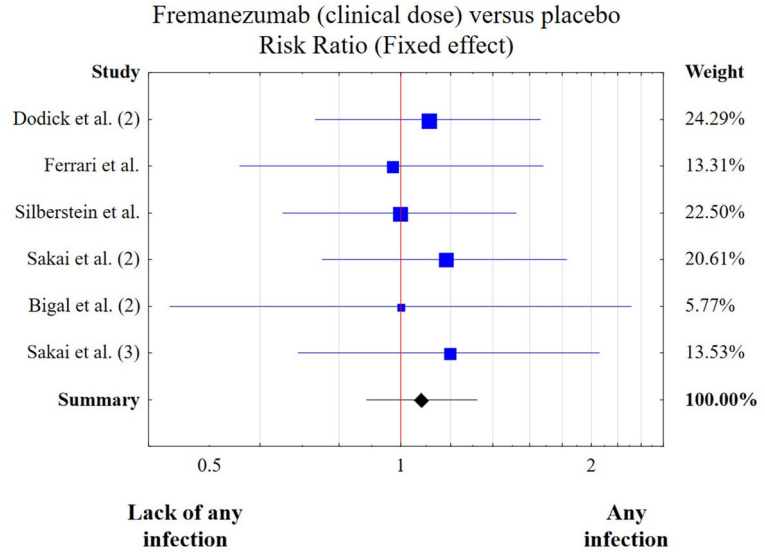

Fig. 3 Risk of any infection in patients treated with clinical doses of fremanezumab vs. placebo

Table 5 Dose and infection-type dependent risk of infection in patients treated with galcanezumab vs. Placebo

Galcanezumab dose	Statistics	Infection				
		Any	Viral	Bacterial	COVID-19	Urinary
Any	*p*- value	0.426	0.632	0.228	0.315	0.226
	RR	1.04	1.02	1.26	0.33	1.31
Clinical	*p*-value	**0.024**	**0.046**	0.317	0.315	0.669
	RR	**1.13**	**1.13**	1.25	0.33	1.13
High	*p*- value	0.855	0.234	0.202	-	0.074
	RR	0.98	0.92	1.35	-	1.61

COVID-19 - Coronavirus disease 2019; UTI– urinary tract infection; RR– risk ratio

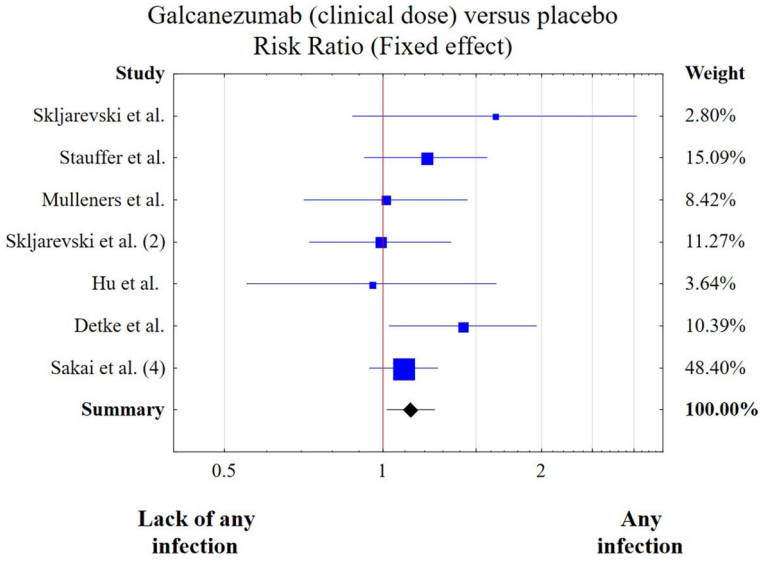

Fig. 4 Risk of any infection in patients treated with clinical doses of galcanezumab vs. placebo

Table 6 Dose and infection-type dependent risk of infection in patients treated with eptinezumab vs. Placebo

Eptinezumab dose	Statistics	Infection				
		Any	Viral	Bacterial	COVID-19	Urinary
Any	*p*- value	0.717	0.599	0.585	0.604	0.421
	RR	1.03	1.04	0.87	1.16	0.81
Clinical	*p*-value	0.472	0.411	0.699	0.604	0.760
	RR	1.06	1.07	0.90	1.16	0.92
High	*p*- value	**0.015**	**0.038**	0.246	0.827	0.439
	RR	**1.23**	**1.21**	1.37	1.08	1.25

COVID-19 - Coronavirus disease 2019; UTI– urinary tract infection; RR– risk ratio

Eptinezumab

The meta-analysis included 6 studies with 3824 participants aged 40.4 years (SD = 10.7). The details of each analysis have been presented in Supplement 4. The studies had low heterogeneity (Q = 1.10, df = 5, $p = 0.954$, $I^2 = 0.00\%$) and their publication bias was also low in funnel plot and Egger's tests (t = 0.484, df = 4, $p = 0.654$). Additionally, the 'trim-and-fil test' did not identify biased trials. L'Abbe and Galbraith diagram analysis showed that particular study results followed the combined effect. Sensitivity analysis did not show that the exclusion of one study from the analysis led to significant RR change.

Eptinezumab has been shown to increase the overall risk of any or viral infections at higher doses (Table 6, Fig. 5). NNH for any infection equals 24 (E1 = 239, E0 = 832, C1 = 197, C0 = 893). In this case, the RR of infection was 1.23 [1.08, 1.40, $p = 0.015$, power of the test calculated post-hoc was 1 - β = 0.82]. In other words, eptinezumab has a small effect on infection risk. No increased infection risk was found for bacterial infections, COVID-19 or UTIs. The results were not significant for registered clinical doses or 'any dose' used. None of the four moderating variables included in the meta-regression had a significant impact on the overall effect of the meta-analysis.

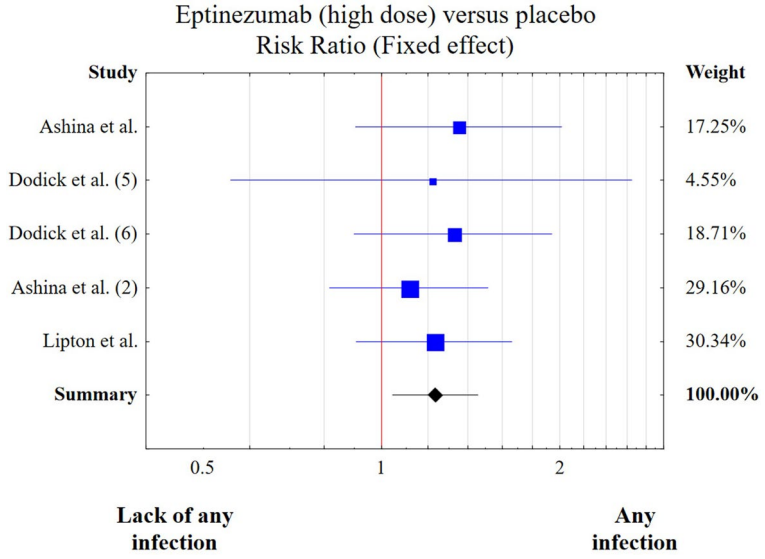

Fig. 5 Risk of any infection in patients treated with higher doses of eptinezumab vs. placebo

Table 7 Dose and infection-type dependent risk of infection in patients treated with Atogepant vs. Placebo

Atogepant dose	Statistics	Infection				
		Any	Viral	Bacterial	COVID-19	Urinary
Any	*p*- value	0.839	0.627	0.285	0.585	0.349
	RR	1.02	0.94	1.33	0.85	1.28
Clinical	*p*-value	0.866	0.655	0.278	0.585	0.344
	RR	1.03	0.95	1.33	0.85	1.29
High	*p*- value	0.866	0.597	0.259	0.585	0.303
	RR	1.02	0.93	1.39	0.85	1.35

COVID-19 - Coronavirus disease 2019; UTI– urinary tract infection; RR– risk ratio

Atogepant and Rimegepant

Due to the limited number of studies for rimegepant, the meta-analysis was possible only for atogepant. It included 4 studies with 2813 participants aged 41.2 years (SD = 1.1). The details of each analysis are presented in Supplement 5. The studies had low heterogeneity (Q = 1.93, df = 3, $p = 0.587$, $I^2 = 0.00\%$) and their publication bias was also low in funnel plot and Egger's tests (t = -0.152, df = 2, $p = 0.893$). Moreover, the 'trim-and-fil test' did not identify biased trials. L'Abbe and Galbraith diagrams analysis showed that particular studies results followed the combined effect. Sensitivity analysis did not show that the exclusion of one study from the analysis led to a significant RR change.

Atogepant has not been shown to increase the risk of viral, bacterial, UTIs and overall infection (Table 7). The results were consistent across 'high', 'registered' (Fig. 6) or 'any' dosing schemes. None of the four moderating variables included in the meta-regression had a significant impact on the overall effect of the meta-analysis.

Meta-analysis for all CGRP-targeting preventive therapeutics

Only two studies included in the meta-analysis showed significant increase of infection risk (RCT10 for erenumab [31] and RCT 25 for galcanezumab [47]) (Fig. 7). Despite that, the meta-analysis showed an increased infection risk in patients treated with CGRP-targeting therapeutics ($p = 0.016$, RR = 1.08 [1.01, 1.14]) with NNH = 287 (E1 = 1893, E0 = 8664, C1 = 1423, C0 = 6670) (Fig. 7). This result was also significant for viral infections (RR = 1.07 [1.00, 1.14]), but not for COVID-19 or bacterial infections or other dosing schemes. The details of each analysis are presented in Supplements 6 and 7. In the sensitivity analysis exclusion of one study from the meta-analysis did not significantly affect the results, but excluding two studies (RCT25 [46] and 26 [47]) lead to loss of significance for the whole meta-analysis (RR = 1.06 [0.99; 1.14]).

Risk of UTIs in people treated with high doses of CGRP-targeting medications was also not increased (RR = 1.31 [0.98, 1.75]) (Fig. 8). However, a sensitivity analysis indicates that excluding RCT1 (erenumab) [22] and RCT12 (fremanezumab) [33] from the meta-analysis

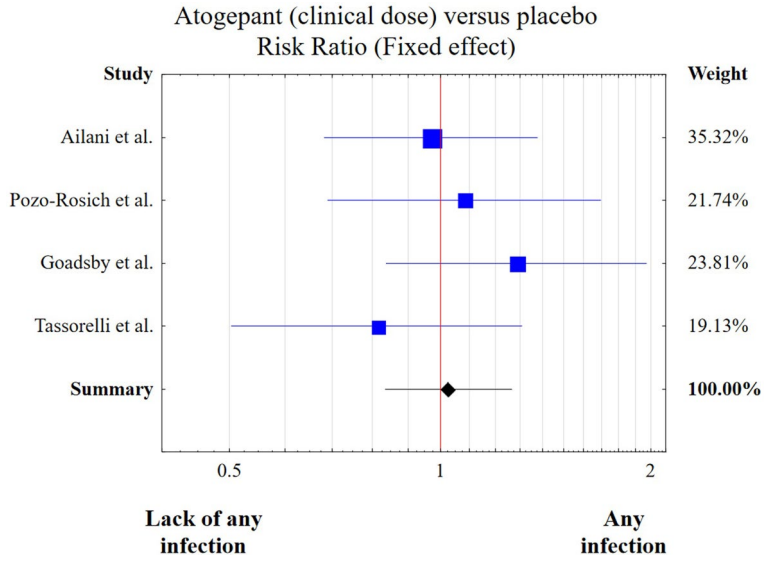

Fig. 6 Risk of any infection in patients treated with clinical doses of atogepant vs. placebo

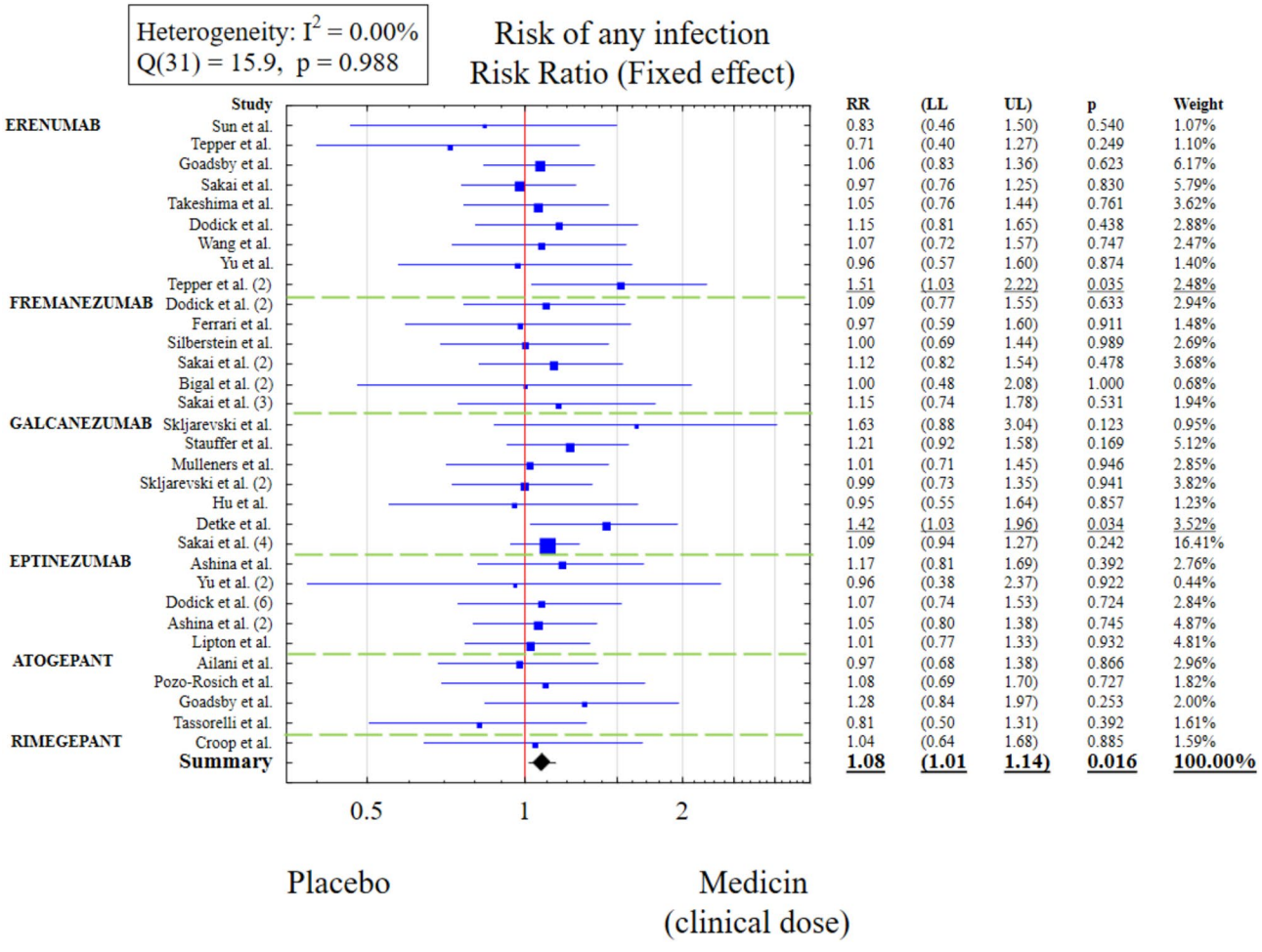

Fig. 7 Risk of any infection in patients treated with clinical doses of CGRP-targeting medications. RR– relative risk, LL– lower limit, UL– upper limit)

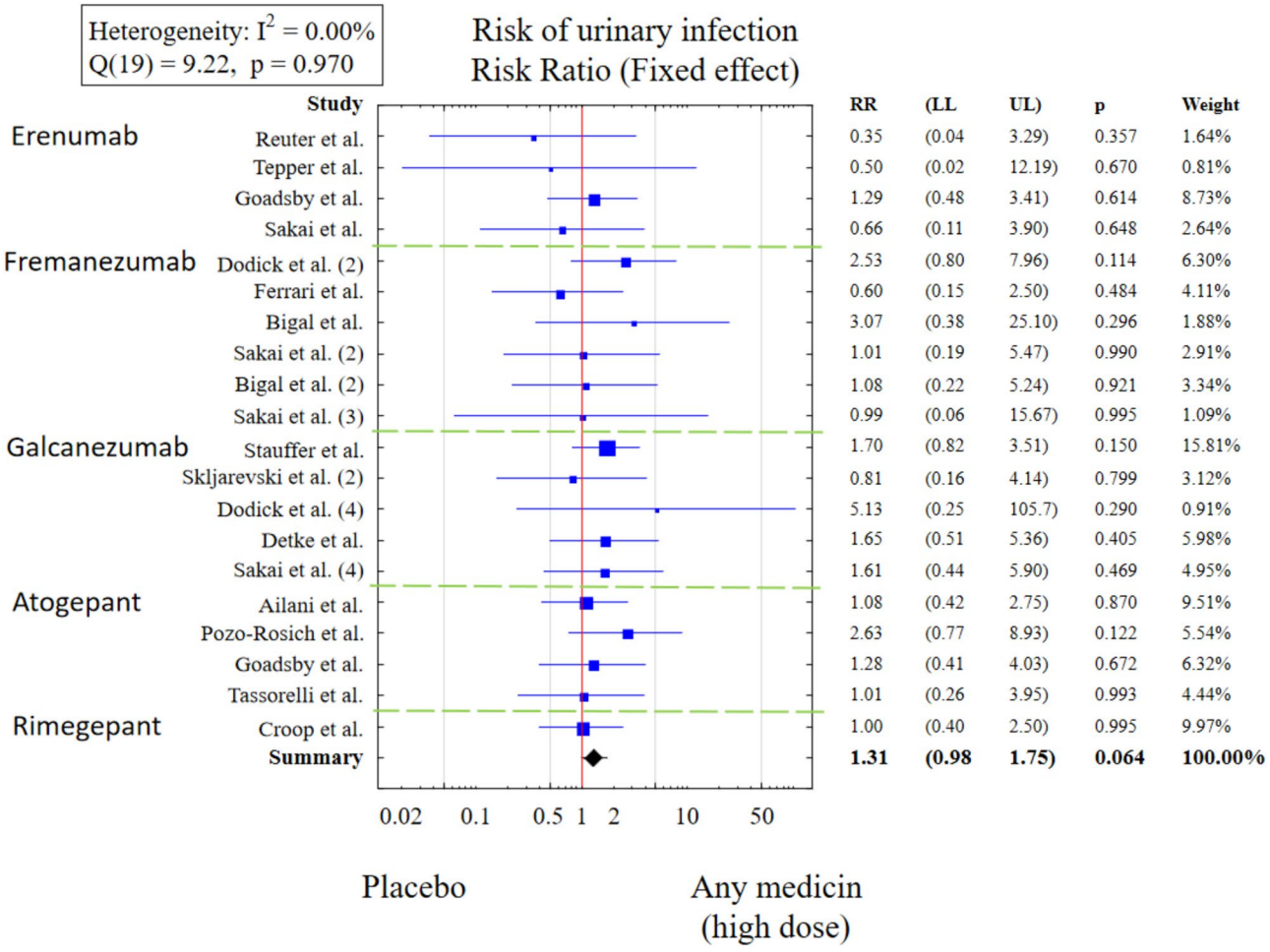

Fig. 8 Risk of urinary tract infections in patients treated with clinical doses of CGRP-targeting medications (RR– relative risk, LL– lower limit, UL– upper limit).

significantly affects the results ($p = 0.029$). After excluding these two publications from the meta-analysis, the risk of urinary tract infections among patients taking any anti-CGRP drug is significantly higher compared to patients taking placebo ($p = 0.029$; RR = 1.39 [1.03, 1.87]). A negative, statistically significant relationship was observed between the logarithm of relative risk for UTIs and the age of patients taking anti-CGRP medications at clinical doses. An increase in the mean age in the study by one year was accompanied by a decrease in the logarithm of RR for UTIs by an average of 0.12.

Infectious SAEs

Database search yielded 30 studies with gastrointestinal, respiratory and genitourinary infectious SAEs being the most often reported complaints (Table 8). Sepsis was reported in 5 instances, with 3 cases in the eptinezumab studies. Among all particles fremanezumab was associated with fewest infectious SAEs ($n = 3$), while erenumab showed highest incidence of these events ($n = 36$). However, it should be underlined that erenumab has far more studies assessing infectious SAEs than any other CGRP-targeting medication.

Discussion

This meta-analysis pools data from randomised placebo-controlled trials and indicates that CGRP-targeting therapies may increase infection risk. However, the overall risk seems to be very low, with NNH as high as 287 and only two studies separately showing higher incidence of infections. In this light, the results should be interpreted carefully.

Only two separate studies showed statistically significant increased infection risk However, the advantage of the meta-analysis is to show weaker associations for which smaller studies are underpowered. To ensure that the observed result is not merely an effect of one positive trial we performed a sensitivity analyses. These showed that excluding any or both of the two of positive trials did not result in loss of significance. However, excluding two studies for galcanezumab (one positive and one negative) lead to that effect. Conversely, UTI risk seems not to be

Table 8 Serious infectious adverse events reported in blinded and open-label trials and real world evidence

	Gastrointestinal	Respiratory	Genitourinary	Skin & connective tissue	Sepsis	Other & unclassified
Erenumab						
NCT03096834	1	1	1	1		
NCT01952574	3	1	1	1		
NCT02456740	3		1	1		1
NCT02630459	4	3				
NCT03812224		1				
NCT02483585	1	1			1	1
NCT03333109	1					
NCT03867201						1
NCT03971071	1					
NCT02174861	1	1				
BASEC ID 2018–02375	2	1				
Fremanezumab						
NCT03308968	1					
NCT02021773		1				
NCT02621931		1				
Galcanezumab						
NCT03559257		2				
NCT02614196		1				
NCT02438826	4					
NCT03963232	1		1	1		
NCT02614261	1	1	2	1		1
NCT02959190		1				
Eptinezumab						
NCT04418765	5	5	1	1	3	
NCT01772524			1			
NCT02275117	1		1			
NCT02974153	1					
Rimegepant						
NCT03266588	2	2		1		1
NCT03732638	1					
Atogepant						
NCT03855137	1	2				
NCT03700320		2			1	1
NCT03939312	2	1				1
NCT02848326	1					
	36	**29**	**10**	**7**	**5**	**7**

Gastrointestinal SAEs: gastroenterocolitis, gastrointestinal tuberculosis, herpes simplex hepatitis, diverticulitis, abdominal abscess, tooth abscess, rectal abscess, peritonitis, anal abscess, Clostridium difficile colitis; respiratory SAEs: pneumonia, mycoplasma infection, pharyngitis, tonsillitis, COVID-19, influenza; genitourinary SAEs: urinary tract infection, pyelonephritis, tubo-ovarian abscess, vaginal abscess; Skin and connective tissue SAEs: cellulitis, erysipelas, infected dermal cyst, pilonidal disease; Sepsis included 1 case of bacteraemia; other and unclassified SAEs: beta-haemolytic streptococcal infection, staphylococcal infection, pericarditis, meningitis, osteomyelitis, mastitis

increased but sensitivity analysis indicated that excluding two studies changed the meta-analysis results from negative to positive. It should be than underlined that the sensitivity analysis does not dismiss the associations found in this meta-analysis but merely underlines that the effect found is small and requires further studies.

It seems that infection risk depends on particular medication, with eptinezumab and galcanezumab being the only drugs with risk increase in particle-specific meta-analysis. Despite negative results for other particles it should be remembered that also erenumab, atogepant and rimegepant have been implicated in increased risk of some infections by other authors [6, 8, 9]. The same has been reported for ubrogepant [59]. In this light, it seems probable that blocking the CGRP pathway may predispose to infections although overall clinical effect will be very small in otherwise healthy migraine patients. Considering small effect of CGRP-targeting medications on infection risk it is also unsurprising that only subthreshold signals were found that this risk depends on medication dosing or pathogen type.

Infection risk depends on a multitude of factors that could not be evaluated by this meta-analysis. For example, upper respiratory tract infection risk increases with social interactions, while migraine burden limits these interactions [60]. It is then possible that improvement with regard to migraine achieved by CGRP targeting therapies might have led to an increased exposure to viruses, which in turn could explain increased infection risk. Apart from that, CGRP-targeting therapies may cause constipation, which in turn is a risk factor of UTIs [61]– a phenomenon that could explain why atogepant was implicated to cause UTIs. Eptinezumab effects could also be related to intravenous administration of this drug and its higher risk of infections than subcutaneous or oral application.

The body's response to an infection or parasitic invasion is inflammation, which may lead to elimination or neutralization of the pathogen. One such mechanism is the production and release of immunomodulatory neuropeptides like CGRP which can be produced by various cell types involved in the response to viruses and bacteria [12]. CGRP can promote anti-, as well as pro-inflammatory processes required for mounting an effective immune response. On one hand, it inhibits antigen presentation, the production of some crucial interleukins (e.g. IL-1β) and chemokines involved in innate immune response, as well as the targeted migration of inflammatory cells [62–66]. On the other hand, it increases the numbers of circulating granulocytes, monocytes and lymphocytes, stimulates mast cells degranulation, as well as promotes certain T-helper lymphocytes subtypes [67, 68]. In this light, CGRP(-R) antagonists may potentially alter these processes with difficult to predict clinical consequences.

In case of viral infections such as COVID-19, CGRP prevents viral replication, propagation and cross-reactivity [14, 69]; this has been especially proven by the Barbosa Bomfim et al. study, which gives biological evidence that blocking the CGRP pathway may promote severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The researchers showed that CGRP can directly prevent SARS-CoV-2 Omicron and Alpha variants from infecting bronchial epithelial cells. This effect was nullified by blocking CGRP receptors with olcegepant. Consequently, CGRP pathway antagonists may potentially increase the risk of COVID-19. This hypothesis has been recently supported by a randomized placebo-controlled trial which demonstrated a more than double risk of SARS-CoV-2 infection in people treated with erenumab [31]. Both of the above described studies indicate that increased COVID-19 risk in people undergoing CGRP-targeting therapies is biologically and clinically plausible. However, it should also be noted that several retrospective studies [70, 71] and our own meta-analysis did not find this association. This may be related to an overall small clinical effect or underreporting of mild cases and low risk of severe COVID-19.

In response to bacterial infection CGRP plays contradictory roles. On the one hand, it potentially contributes to bacterial infections by inhibiting innate immune response and reaction to Gram-negative microbes [15, 72–74]. On the other hand, CGRP shows antimicrobial activity and increases the production of protective mucous as well as elimination of the digested pathogenic bacteria [75, 76]. Furthermore, it may play a role in protecting tissue against damage during sepsis [77]. In this light, CGRP-pathway antagonists may influence mutually contradictory mechanisms and cause little net effect. This might be why no significant safety signals where identified by our meta-analysis.

Safety concerns for CGRP-targeting therapies have been pointed out by some authors [78, 79]. When interpreting the results of this meta-analysis readers should also take into account that it focuses mostly on otherwise healthy migraine patients. People with 'any clinically significant hematologic, endocrine, pulmonary, renal, hepatic, gastrointestinal, or neurologic disease' were barred from participation. In other words, some populations vulnerable to infection were underrepresented: elderly participants, people on immunosuppressive therapies, patients with acquired immunodeficiency, chronic disorders affecting susceptibility to infections like diabetes, chronic kidney disease, chronic obstructive pulmonary disease or severe cardiovascular disorders. However, the prevalence of migraine in these populations remains significant [80] and their increased use of CGRP-targeting therapies can be anticipated. Moreover, in most trials the placebo-controlled phase lasted 3 months. This timeframe could be insufficient to identify increased infection risk if CGRP(-R) antagonists cause immunosuppression developing over a longer period.

Limitations

While the findings of this meta-analysis are based on high-quality evidence from randomized placebo-controlled trials, the limited number of studies and short duration of placebo-controlled phases should be taken into account when interpreting the results. It should also be noted that some particles (e.g. erenumab) have considerably more studies assessing infectious AEs than others (e.g. rimegepant). Therefore, it is impossible to compare the infection risk between included medications. Future research with more trials and diverse populations would help provide more robust and generalizable conclusions.

This meta-analysis assesses the infection risk in RCTs designed to test drug efficacy. In other words, the included trials were not specified to systematically evaluate infection incidence. Consequently, a bias

of underreporting of infections should be expected, especially with regard to mild disorders self-treated by 78–95% patients [81]. Moreover, included studies differed with regard to recruited populations and diagnoses. It is therefore possible that unidentified factors contributed to the obtained results.

Conclusions

The wide systemic distribution of CGRP and its receptor, as well as the involvement of CGRP in many immunological processes, indicate the role of this neuropeptide in maintaining pathogen immunity against all major groups of infective agents. In this meta-analysis CGRP-targeting medications have a statistically significant but clinically weak effect on the increase in infection risk. These results should be interpreted carefully, considering that only few studies showed significant infection risk. Consequently, a CGRP pathway block may be insignificant to the majority of patients, and would rarely contribute to serious adverse reactions in populations without comorbidities affecting immunity. However, increased infection risk may prove to be important to healthcare systems when considering the high prevalence of migraine and increasing popularity of CGRP-targeting therapies. Further studies are needed to assess the safety of these medications, especially in immunocompromised patients (e.g. on immunosuppressive therapies).

Abbreviations

CGRP	Calcitonin gene-related peptide
COVID-19	Coronavirus disease 2019
EER	Percentage of participants in the experimental group who experienced an adverse effect (infection)
NNH	Number Needed to Harm
RD	Risk Difference
RR	Relative risk
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
UTI	Urinary tract infection

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

Supplementary Material 8

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Author contributions

MS: project concept, project coordination, protocol draft and registration, database search, data extraction and analysis, risk of bias assessment, writing final manuscript. DK: studies selection and data extraction. KM: studies selection and data extraction, review of the meta-analysis and final manuscript. BB: statistical analysis coordination, review of the final manuscript. EKW: literature search and writing WK: literature search and writing. BM: review of statistical analysis project and review of the meta-analysis, review of the final manuscript. MWP: review of study concept and the final manuscript. AM: review of study concept and the final manuscript.

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Data availability

The datasets generated and/or analysed during the current study are available in the public repository: https://figshare.com/articles/dataset/CGRP_targeting_therapies_may_increase_infection_risk_a_meta-analysis_of_placebo-controlled_trials_and_a_narrative_review/28375523/1.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

MS reports personal fees from Pfizer, Teva, Bausch, AbbVie, Neuca and Novartis for speaker activities. DK reports no competing interests. KM reports no competing interests. BB reports no competing interests. EKW reports no competing interests. WK reports no competing interests. BM reports no competing interests. KPP reports no competing interests. MW-P is member of Editorial Board: The Journal of Headache and Pain; reports personalfees from Abb. Vie, Pfizer, Polpharma and Teva for speaker activities. AM reports personal fees from Novartis, Betapharm, TEVA and Ipsen for speaker activities or advisory boards.

Author details

[1]Department of Family Medicine and Infectious Diseases, University of Warmia and Mazury in Olsztyn, Warszawska 30, Olsztyn 10-082, Poland
[2]Scientific Section of the Polish Society of Family Medicine, Syrokomli 1, Wroclaw 51-141, Poland
[3]Department of Neurology, Wroclaw Medical University, Borowska 213, Wroclaw 50-556, Poland
[4]Department of Pathophysiology and Immunology, National Institute of Geriatrics, Rheumatology and Rehabilitation, Spartanska 1, Warsaw 02-637, Poland
[5]Department of Psychiatry, Wroclaw Medical University, Pasteura 10, Wroclaw 50-367, Poland
[6]Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, Martinistraße 52, 20251 Hamburg, Germany

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