ORIGINAL RESEARCH ARTICLE

Drug Safety 2008; 31 (7): 627-636
0114-5916/08/0007-0627/$48.00/0

Occurrence of Community-Acquired Respiratory Tract Infection in Patients Receiving Esomeprazole

Retrospective Analysis of Adverse Events in 31 Clinical Trials

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Abstract

Background: A potential causal association between an increase in gastric pH and a risk of community-acquired respiratory tract infection (RTI), specifically pneumonia, has been debated in relation to the use of potent gastric acid-suppressive medication.

Objective: To investigate the occurrence of community-acquired RTI, including pneumonia, in patients receiving esomeprazole versus placebo and other acid-suppressive agents in randomized clinical trials.

Methods: The AstraZeneca ARIADNE safety database was searched for comparative, controlled phase II–IV randomized, blinded clinical studies with esomeprazole and standard reporting of all adverse events (AEs). Pooled AE data were presented according to treatment comparison (esomeprazole versus placebo, esomeprazole 40 mg versus 20 mg daily, esomeprazole versus omeprazole, lansoprazole and/or ranitidine, respectively). Frequency and relative risk (RR), with 99% confidence interval (CI) and adjustment for time on treatment, were calculated for the following four AE categories: all RTIs; signs and symptoms potentially indicating RTI; lower RTI; and pneumonia.

Results: Thirty-one studies were identified, in which 16 583 patients received esomeprazole and 12 044 patients received either placebo or comparator acid-suppressive drugs. The occurrence of all four categories of AEs was similar between esomeprazole and placebo (all RTIs: 9.2% versus 8.5%; signs and symptoms of RTI: 1.8% versus 1.8%; lower RTI: 1.6% versus 1.5%; and pneumonia: 0.2% in both groups). The RR estimates were as follows: all RTIs, 0.93 (99% CI 0.78, 1.11); signs and symptoms of RTI, 0.85 (99% CI 0.57, 1.27); lower RTI, 0.92 (99% CI 0.59, 1.42); and pneumonia, 0.94 (99% CI 0.29, 3.07). The distribution of RTIs by patient sex and age showed a similar pattern in esomeprazole and placebo-treated patients. The comparisons of esomeprazole with the other comparator acid-suppressive drugs showed a similar pattern with only minor numerical differences in the occurrence of RTI between the drugs. There were no significant between-group differences with esomeprazole versus placebo for all four categories of AEs according to esomeprazole dosage, treatment indication and duration of treatment.

Conclusions: This pooled analysis found no causal association between acid-suppressive therapy with esomeprazole and increased risk of community-acquired RTI, including pneumonia, in patients receiving this agent for gastric acid-related disorders.

Background

A potential causal association between an increase in gastric pH and a risk of respiratory tract infection (RTI), specifically pneumonia, has been debated in relation to the use of potent gastric acid-suppressive medication.[1-8] For example, in one large cohort study the adjusted relative risk (RR) for pneumonia among patients currently using proton pump inhibitors (PPIs) compared with those who had stopped using PPIs was 1.89 (95% CI 1.36, 2.62).[3] This association is hypothesized to be related to the increase in gastric pH with acid-suppressive therapy, which may result in colonization of the oral cavity by intestinal pathogens. However, other authors have questioned the causal link between the use of acid-suppressive agents and RTIs such as pneumonia, suggesting that characteristics common in patients receiving acid-suppressive therapy (such as smoking, alcohol consumption and obesity) may play a contributory role.[6-8]

Esomeprazole is a PPI indicated for a variety of gastric acid-related conditions. In this study, we report the findings from a retrospective analysis of pooled adverse event (AE) data designed to investigate the occurrence of community-acquired RTI, including pneumonia, in patients receiving esomeprazole versus placebo and other acid-suppressive agents in randomized clinical trials.

Methods

Study Design

The present study is based on pooled AE data from randomized clinical trials with esomeprazole in the AstraZeneca ARIADNE database. From the overall pool, data from sub-pools, based on, for example, head-to-head comparisons of drugs, are analysed.

The AstraZeneca ARIADNE safety database contains data from pivotal studies of major importance to the drug development and regulatory approval process. The methods for collecting, standardizing and compiling safety-related data in these studies have been consistent over time. In an effort to extract high-quality data from prospective head-to-head trials, we searched the database for comparative phase II–IV clinical studies of esomeprazole and placebo or other acid-suppressing agents, with standard reporting of all AEs (i.e. non-serious as well as serious AEs).

All studies that met these criteria, a total of 31 randomized, double-blind, placebo- or active-controlled clinical studies, performed from 1998 to 2007, were selected (see tables I, II and III). The studies included patients with gastro-oesophageal reflux disease (GORD), NSAID-associated peptic ulcer or gastrointestinal symptoms, dyspepsia or reflux asthma.

The primary analyses are based on the esomeprazole versus placebo comparison as a means to study a potential effect of acid suppression on the occurrence of RTI. In addition, analyses of esomeprazole in relation to other PPIs (omeprazole and lansoprazole) and the histamine H_2 receptor antagonist ranitidine are included to investigate the possibility of any drug-specific effect.

Endpoints

From the pooled clinical trial population, the occurrence of the following AEs was calculated based on MedDRA® (Medical Dictionary for Regulatory Activities, version 8.1; Northrop Grumman, Reston, VA, USA) terms, including: all RTIs (MedDRA high-level term 'respiratory tract infections'); signs and symptoms potentially indicating a RTI (MedDRA high-level terms 'lower respiratory tract signs and symptoms', 'upper respiratory tract signs

Table I. Design details of clinical trials of esomeprazole included in the analysis (indication gastro-oesophageal reflux disease)

Study number and reference	Design	Esomeprazole regimen (no. of pts)	Comparator regimen (no. of pts)	Duration
SH-QBE-0010[9]	r, db, pg	40 mg prn (292) 20 mg prn (279)	Placebo prn (146)	6 mo
SH-QBE-0012[10]	r, db, pg	40 mg prn (184)	Placebo prn (187)	6 mo
SH-QBE-0014[11]	r, db, pg	40 mg od (92) 20 mg od (98) 10 mg od (91)	Placebo od (92)	6 mo
SH-QBE-0015[12]	r, db, pg	40 mg od (81) 20 mg od (81) 10 mg od (76)	Placebo od (77)	6 mo
SH-QBE-0022[13]	r, db, pg	20 mg prn (170)	Placebo prn (171)	6 mo
SH-QBE-0053[14]	r, db, pg	40 mg od (122) 20 mg od (120)	Placebo od (123)	4 wk
SH-QBE-0054[14]	r, db, pg	40 mg od (116) 20 mg od (112)	Placebo od (117)	4 wk
SH-QBE-0065[15]	r, db, pg	40 mg od (170) 20 mg bid (174)	Placebo od (92)	4 wk
SH-QBE-0009[16]	r, db, pg	40 mg od (424) 20 mg od (418)	OME 20 mg od (435)	4 wk
SH-QBE-0011[16]	r, db, pg	40 mg od (346)	OME 20 mg od (343)	4 wk
SH-QBE-0013[17]	r, db, pg	40 mg od (653) 20 mg od (655)	OME 20 mg od (649)	8 wk
SH-QBE-0016[18]	r, db, pg	40 mg od (576)	OME 20 mg od (571)	8 wk
SH-QBE-0017[19]	r, db, pg	20 mg od (585)	OME 20 mg od (588)	8 wk
SH-QBE-0021[16]	r, db, pg	20 mg od (336)	OME 20 mg od (334)	4 wk
SH-QBE-0052[20]	r, db, pg	40 mg od (1205)	OME 20 mg od (1200)	8 wk
D9612L00046[21]	r, db, pg	40 mg od (498)	LAN 30 mg od (501)	8 wk
D9612L00048[22]	r, db, pg	40 mg od for healing (1168), 20 mg od for maintenance (509)	LAN 15 mg od for maintenance (511)	4–8 wk healing[a] + 6 mo of maintenance
SH-QBE-0067[23]	r, db, pg	40 mg od for healing (1385), 20 mg od for maintenance (617)	LAN 15 mg od for maintenance (614)	4–8 wk healing[a] + 6 mo of maintenance
SH-QBE-0083[24]	r, db, pg	40 mg od (2620)	LAN 30 mg od (2608)	8 wk
SH-QBE-0069[25]	r, db, pg	40 mg od (51)	RAN 150 mg bid (52)	4 wk

a Non-comparative treatment period, not included in analysis.

bid = twice daily; **db** = double blind; **LAN** = lansoprazole; **od** = once daily; **OME** = omeprazole; **pg** = parallel group; **prn** = when required (on demand); **pts** = patients; **r** = randomized; **RAN** = ranitidine.

and symptoms' or the preferred terms 'lower respiratory tract inflammation' or 'pneumonitis'); lower RTI (MedDRA high-level terms 'bacterial lower respiratory tract infections', 'fungal lower respiratory tract infections', 'lower respiratory tract infections NEC', 'parasitic lower respiratory tract infections' or 'viral lower respiratory tract infections'); and pneumonia (the reported pneumonia terms in the analysed studies, i.e. the MedDRA preferred terms 'bronchopneumonia', '*pneumocystis jiroveci* pneumonia' and 'pneumonia').

Pooled AE data for all studies were presented according to treatment type (esomeprazole versus placebo, omeprazole, lansoprazole or ranitidine, respectively, and esomeprazole 40 mg versus 20 mg daily). Data for placebo-controlled studies were presented by treatment indication (GORD, NSAID-associated peptic ulcer or gastrointestinal symptoms, dyspepsia or reflux asthma), patient age (<65 versus ≥65 years), sex and according to short-term or long-term treatment duration (4–8 weeks or 16–26 weeks, respectively).

Table II. Design details of clinical trials of esomeprazole included in the analysis (indication NSAID-associated ulcer/upper gastrointestinal symptoms)

Study number and reference	Design	Esomeprazole regimen (no. of pts)	Comparator regimen (no. of pts)	Duration (wk)
SH-NEN-0001[26]	r, db, pg	40 mg od (205) 20 mg od (194)	Placebo od (207)	4
SH-NEN-0002[27]	r, db, pg	40 mg od (106) 20 mg od (110)	Placebo od (117)	26
SH-NEN-0003[26]	r, db, pg	40 mg od (177) 20 mg od (187)	Placebo od (189)	4
SH-NEN-0004[27]	r, db, pg	40 mg od (90) 20 mg od (92)	Placebo od (94)	26
SH-NEN-0013[28]	r, db, pg	40 mg od (196) 20 mg od (192)	Placebo od (185)	26
SH-NEN-0014[28]	r, db, pg	40 mg od (276) 20 mg od (272)	Placebo od (269)	26
SH-NEN-0005[29]	r, db, pg	40 mg od (131) 20 mg od (140)	RAN 150 mg bid (133)	8
SH-NEN-0006[30]	r, db, pg	40 mg od (140) 20 mg od (145)	RAN 150 mg bid (147)	8

bid = twice daily; **db** = double blind; **od** = once daily; **pg** = parallel group; **pts** = patients; **r** = randomized; **RAN** = ranitidine.

Statistical Analysis

Rates of occurrence of AEs were presented as the percentage of patients with a particular event (or group of events) in relation to all patients in the exposure groups. The total number of patients with any event per treatment-year was also reported.

RR values, adjusted for treatment duration (time-adjusted), were calculated for each group of events. Descriptive 99% confidence intervals (CIs) were calculated using SAS® software (version 8.02; SAS Institute Inc., Cary, NC, USA). A 99% CI was chosen as a pre-specified means to compensate for the multiple comparisons performed.

Results

A total of 16 583 patients were exposed to esomeprazole for 2957.9 patient-years, and 12 044 patients received either placebo (n = 3358), omeprazole (n = 4120), lansoprazole (n = 4234) or ranitidine (n = 332) for a total of 1923.2 patient-years. The demographic characteristics of patients included in the analysis are described, by treatment group, in table IV. Overall, patient age ranged from 18 to 89 years, with a median age of 48 years for esomeprazole-treated patients and 47 years for the placebo or active comparator groups. Treatment groups were also comparable in terms of sex distribution. Between-group differences in mean treatment duration were adjusted for in the RR calculations.

In the esomeprazole (n = 6534) versus placebo (n = 3358) pool, patients were treated for a total of 1631 and 719 patient-years, respectively. The sex distribution was similar in the two groups as was the age distribution, with a mean age of 50 years and 18% of patients being ≥65 years of age.

Table III. Design details of clinical trials of esomeprazole included in the analysis (indication dyspepsia and reflux asthma)

Study number and reference	Design	Esomeprazole regimen (no. of pts)	Comparator regimen (no. of pts)	Duration (wk)
Dyspepsia				
SD-NED-0021[31]	r, db, pg	40 mg od (1020)	Placebo od (504)	7
SD-NED-0022[32]	r, db, pg	40 mg od (773)	Placebo od (407)	7
Reflux asthma				
SD-NEE-0003[33]	r, db, pg	40 mg bid (386)	Placebo bid (381)	16

bid = twice daily; **db** = double blind; **od** = once daily; **pg** = parallel group; **pts** = patients; **r** = randomized.

Table IV. Demographics of patients (pts) included in the analysis

Pts	ESO vs PL (17 studies)		ESO vs OME (7 studies)		ESO vs LAN (4 studies)		ESO vs RAN (3 studies)		ESO20 vs ESO40 (14 studies)	
	ESO	PL	ESO	OME	ESO	LAN	ESO	RAN	ESO20	ESO40
No. of pts	6534	3358	5198	4120	4244	4234	607	332	2816	2809
No. of treatment-years	1631.0	719.3	468.3	387.5	772.0	771.5	86.5	44.9	535.8	536.2
Sex [n (%)]										
Male	2442 (37.4)	1228 (36.6)	2900 (55.8)	2372 (57.6)	2520 (59.4)	2490 (58.8)	199 (32.8)	115 (34.6)	1136 (40.3)	1121 (39.9)
Female	4092 (62.6)	2130 (63.4)	2298 (44.2)	1748 (42.4)	1724 (40.6)	1744 (41.2)	408 (67.2)	217 (65.4)	1680 (59.7)	1688 (60.1)
Ethnicity [n (%)]										
White	2979 (91.5)	3041 (90.6)	4878 (93.8)	3918 (95.1)	3790 (89.3)	3779 (89.3)	510 (84.0)	274 (82.5)	2550 (90.5)	2532 (90.1)
Black	215 (3.3)	110 (3.3)	221 (4.3)	149 (3.6)	212 (5.0)	221 (5.2)	28 (4.6)	20 (6.0)	121 (4.3)	138 (4.9)
Asian	127 (1.9)	58 (1.7)	23 (0.4)	14 (0.3)	21 (0.5)	31 (0.7)	38 (6.2)	17 (5.1)	55 (2.0)	51 (1.8)
Other	213 (3.3)	149 (4.4)	76 (1.5)	39 (0.9)	221 (5.2)	293 (6.9)	31 (5.1)	21 (6.3)	90 (3.2)	90 (3.2)
Age										
Mean, y (range)	50.3 (18–89)	50.8 (18–89)	46.7 (18–83)	47.0 (18–84)	47.5 (18–85)	47.7 (18–84)	57.2 (18–86)	56.1 (19–88)	52.3 (18–89)	52.5 (18–88)
≥65 y, n (%)	1203 (18.4)	620 (18.5)	591 (11.4)	496 (12.0)	483 (11.4)	501 (11.8)	200 (32.9)	98 (29.5)	667 (23.7)	680 (24.2)

ESO = esomeprazole; **ESO20** = esomeprazole 20 mg daily; **ESO40** = esomeprazole 40 mg daily; **LAN** = lansoprazole; **OME** = omeprazole; **PL** = placebo; **RAN** = ranitidine.

Esomeprazole versus Placebo

The number of events per treatment-year and time-adjusted RR of any of the four categories of RTI events were similar in the overall esomeprazole versus placebo comparison (table V and figure 1). RRs for all RTIs were 0.93 (99% CI 0.78, 1.11), for signs and symptoms potentially indicating a RTI 0.85 (99% CI 0.57, 1.27), for lower RTI 0.92 (99% CI 0.59, 1.42) and for pneumonia 0.94 (99% CI 0.29, 3.07).

The sub-analyses by sex and age present a corresponding pattern as in the overall analysis, with only minor numeric differences between esomeprazole and placebo for males and females as well as for patients <65 years and ≥65 years of age (figure 1).

Dividing the esomeprazole versus placebo pool into short-term (4–8 weeks) and long-term (16–26 weeks) treatment reveals a slightly different pattern in the RR point estimates compared with the overall result (table V, figure 2). However, considering the wide CIs, it is not possible to draw any conclusions from these numeric differences. Similarly, a division based on indication for treatment, i.e. GORD, NSAID-associated peptic ulcer or gastrointestinal symptoms, dyspepsia and reflux asthma, does not give support for a difference in the occurrence of any of the four RTI categories between esomeprazole and placebo treatment in these subpopulations (figure 3).

Esomeprazole 40 mg versus 20 mg Daily

The analysis of the head-to-head dose comparisons of esomeprazole 40 mg versus esomeprazole 20 mg daily did not show a dose-dependent difference in the occurrence of any of the RTI categories (table V).

Esomeprazole versus other Acid-Suppressive Therapy

The frequency and time-adjusted RR of any of the four categories of RTI events was similar with esomeprazole compared with omeprazole, lansoprazole or ranitidine, respectively, and the analy-

Table V. Frequency and time-adjusted relative risk (RR) of any respiratory tract infection (RTI), signs and symptoms potentially indicating an RTI, lower RTI or pneumonia, for esomeprazole (ESO) vs placebo (PL), omeprazole (OME), lansoprazole (LAN) or ranitidine (RAN) and esomeprazole 20 mg daily (ESO20) vs esomeprazole 40 mg daily (ESO40)

Group (n)	Any RTI			Signs and symptoms of a RTI			Lower RTI			Pneumonia		
	pts [n (%)]	frequency[a]	RR (99% CI)	pts [n (%)]	frequency[a]	RR (99% CI)	pts [n (%)]	frequency[a]	RR (99% CI)	pts [n (%)]	frequency[a]	RR (99% CI)
Pooled data												
ESO (6534)	602 (9.2)	0.37	0.93 (0.78, 1.11)	120 (1.8)	0.07	0.85 (0.57, 1.27)	104 (1.6)	0.06	0.92 (0.59, 1.42)	15 (0.2)	0.009	0.94 (0.29, 3.07)
PL (3358)	286 (8.5)	0.40		62 (1.8)	0.09		50 (1.5)	0.07		7 (0.2)	0.010	
ESO20 (2816)	210 (7.5)	0.39	0.98 (0.77, 1.25)	47 (1.7)	0.09	1.09 (0.64, 1.88)	29 (1.0)	0.05	0.74 (0.40, 1.39)	4 (0.1)	0.007	0.80 (0.14, 4.50)
ESO40 (2809)	214 (7.6)	0.40		43 (1.5)	0.08		39 (1.4)	0.07		5 (0.2)	0.009	
Short-term (4–8 wk treatment)												
ESO (3370)	192 (5.7)	0.56	0.94 (0.69, 1.28)	41 (1.2)	0.12	0.75 (0.40, 1.42)	34 (1.0)	0.10	1.53 (0.63, 3.73)	6 (0.2)	0.018	2.98 (0.18, 48.0)
PL (1639)	101 (6.2)	0.60		27 (1.7)	0.16		11 (0.7)	0.06		1 (0.1)	0.006	
Long-term (16–26 wk treatment)												
ESO (3164)	410 (13.0)	0.32	0.95 (0.76, 1.17)	79 (2.5)	0.06	0.96 (0.57, 1.61)	70 (2.2)	0.05	0.77 (0.46, 1.27)	9 (0.3)	0.007	0.64 (0.16, 2.48)
PL (1719)	185 (10.8)	0.34		35 (2.0)	0.06		39 (2.3)	0.07		6 (0.4)	0.011	
ESO (5198)	346 (6.7)	0.74	1.17 (0.95, 1.44)	104 (2.0)	0.22	1.01 (0.70, 1.47)	31 (0.6)	0.07	1.03 (0.51, 2.05)	5 (0.1)	0.011	2.07 (0.24, 17.8)
OME (4120)	245 (6.0)	0.63		85 (2.1)	0.22		25 (0.6)	0.06		2 (0.1)	0.005	
ESO (4244)	243 (5.7)	0.31	0.84 (0.67, 1.04)	78 (1.8)	0.10	0.95 (0.63, 1.42)	38 (0.9)	0.05	0.84 (0.48, 1.48)	4 (0.1)	0.005	0.44 (0.09, 2.08)
LAN (4234)	290 (6.9)	0.38		82 (1.9)	0.11		45 (1.1)	0.06		9 (0.2)	0.012	
ESO (607)	20 (3.3)	0.23	0.58 (0.25, 1.31)	6 (1.0)	0.07	1.04 (0.17, 6.35)	4 (0.7)	0.05	0.41 (0.07, 2.31)	0	0	NA
RAN (332)	18 (5.4)	0.40		3 (0.9)	0.07		5 (1.5)	0.11		0	0	

a Number of pts with the event per treatment-year.

NA = not applicable; **PL** = placebo; **pts** = patients.

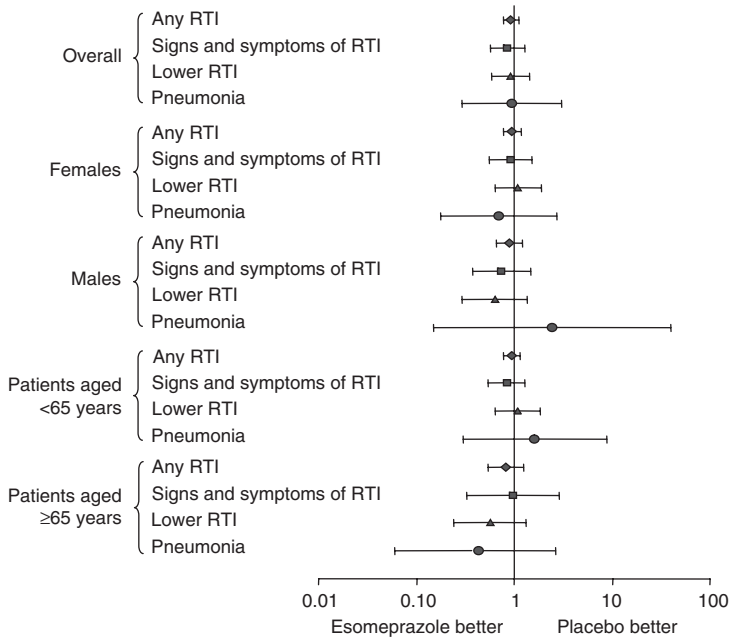

Fig. 1. Time-adjusted relative risk of respiratory tract infection (RTI), potential signs and symptoms of a RTI, lower RTI or pneumonia with esomeprazole vs placebo, overall and according to sex and age. T-bars represent descriptive 99% CI.

ses did not indicate the presence of any drug-specific effects on the occurrence of RTI (table V).

Discussion

This pooled, retrospective analysis of AE data from 31 randomized clinical studies found no causal relationship between treatment with esomeprazole and the risk of RTI, including pneumonia, in patients with gastric-acid related disorders. Indeed, compared with placebo, the frequency of RTI (or potential signs and symptoms of a RTI) among esomeprazole recipients was no higher than expected based on the background incidence of these conditions. The frequency of pneumonia among esomeprazole recipients in our analysis was also similar to that already reported in international population studies, which have estimated the annual incidence of community-acquired pneumonia at 0.5–1.1%.[34,35]

Furthermore, this analysis found that treatment duration and indication did not affect the incidence or risk of RTI occurrence; rates reported with es-

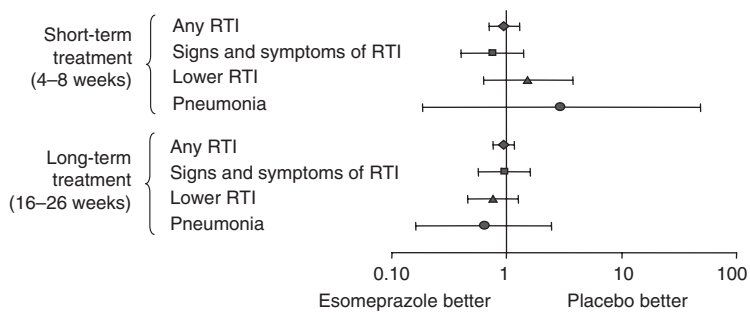

Fig. 2. Time-adjusted relative risk of respiratory tract infection (RTI), potential signs and symptoms of a RTI, lower RTI or pneumonia with esomeprazole vs placebo, according to duration of treatment. T-bars represent descriptive 99% CI.

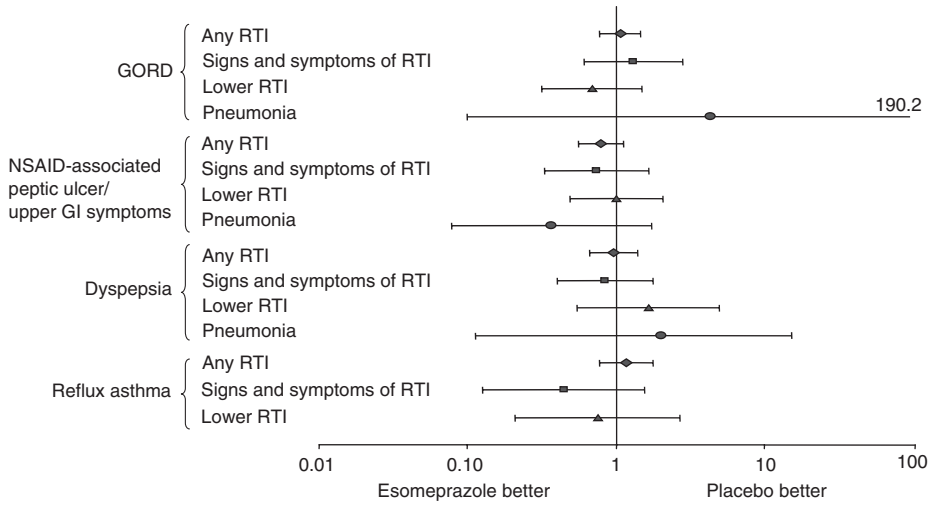

Fig. 3. Time-adjusted relative risk of respiratory tract infection (RTI), potential signs and symptoms of a RTI, lower RTI or pneumonia with esomeprazole vs placebo, according to treatment indication. No case of pneumonia was reported in the reflux asthma sub-pool. T-bars represent descriptive 99% CI. **GI** = gastrointestinal; **GORD** = gastro-oesophageal reflux disease.

omeprazole were similar to those occurring with placebo. Nor did the analysis reveal a different pattern between esomeprazole and placebo for male or female patients or patients <65 or ≥65 years of age. Analyses by dose of esomeprazole or between esomeprazole and other acid-suppressive drugs showed no dose- or drug-specific differences in the occurrence of RTIs.

Overall, the findings of the present analysis contrast with those of previous studies in which patients receiving acid-suppressive therapy appeared to be at risk of community-acquired RTI, including pneumonia.[1-5] In our study, data from controlled, randomized and blinded clinical trials have been analysed, which makes potential influence from unknown and uncontrollable between-group differences, in particular confounding by indication, less likely to bias the results compared with that which may occur with other study designs.

A limitation in using only data from randomized AstraZeneca clinical trials is the potential risk for selection bias in that patients with certain severe concurrent diseases are excluded and only data on patients that fulfil the criteria for participation in the study are analysed. Including any additional, non-AstraZeneca, randomized, controlled clinical studies with esomeprazole in the present pooled analysis was not possible due to factors such as data consistency, for example variable definitions and data collection methods, and access to full data sets.

Given that a 'true' AE of the drug, a drug-related RTI in this case, and not only the symptom/disease as such, is more likely to occur in a category of patients that are not eligible for inclusion in the study than it is in the study subjects, this selection could lead to an underestimation of the risk (and vice versa). The effect on the analysis of AEs of the incongruity between, for example, the population exposed to esomeprazole or placebo in clinical trials and the population treated with esomeprazole in general practice is poorly studied. However, it can be assumed that the difference between the study and general populations is at its maximum when the inclusion and exclusion criteria are assessed, i.e. at randomization, and that it diminishes by time of follow-up in the study.[36]

It should also be noted that a number of subgroup analyses were performed in this evaluation. Calculation of descriptive 99% CIs was chosen as a means of compensation for these multiple comparisons. However, application of a descriptive 95% CI instead of 99% CI gave only minor numeric differ-

ences and did not alter the interpretation of the results.

Conclusions

This pooled, retrospective analysis shows no statistically significant relationship between acid-suppressive therapy with esomeprazole and the risk of community-acquired RTI, including pneumonia, in patients receiving this agent for gastric acid-related disorders.

Acknowledgements

The authors are employees of AstraZeneca (the manufacturer of esomeprazole), who provided financial support for this study. The authors own a limited number of shares in AstraZeneca. We thank Vicki Oldfield and Steve Winter, from Wolters Kluwer Health, who provided medical writing support, funded by AstraZeneca.

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