AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Not applicable
ACTIVE INGREDIENT: Not applicable

Study No: NIS-GGR-DUM-2010/1
A cross-sectional study on the prevalence and extraesophageal symptoms of GERD in patients with upper GI symptoms, visiting the outpatient departments of peripheral hospitals in Greece. **The 'GERDQ-XS' Study**

Developmental Phase: NIS
Study Completion Date: 31/03/2011
Date of Report: 17/02/2012

OBJECTIVES:

Primary objective

- The primary objective of this study was to provide data on the GERD prevalence, expressed as the percentage of patients with upper GI symptoms that will be diagnosed with GERD using the GerdQ questionnaire (GerdQ score ≥ 8).

Secondary objectives

- Estimation of GERD prevalence based on the symptoms reported by the patients to their physician.
- Observation of possible variations between the two specific diagnostic methods (report of the symptoms to the physician and completion of GerdQ questionnaire).
- Recording of the way that potential antisecretory treatment is administered and assessment of patients' compliance to antisecretory treatment (if applicable).
- Assessment of the percentage of GERD patients that may require alterations of their antisecretory treatment (response to treatment).
- Assessment of the prevalence of extraesophageal symptoms using the XQS questionnaire.
- Evaluation of the potential association between GerdQ and XQS scores.

METHODS:

Study design

The present was a multicentre, epidemiological, cross-sectional observational study of patients with upper GI tract symptoms, who presented at the outpatient clinics of regional general hospitals (excluding Athens and Thessaloniki). In total, 18 hospital centres participated in the present study.

Each investigator completed a Case Report Form (CRF) for the first 30 consecutive patients that visited the outpatient clinic of the hospital and fulfilled inclusion/exclusion criteria for study enrolment.

The patient reported outcomes (PRO) for the present study included GerdQ questionnaire and XQS. Each patient of the study completed both GerdQ and XQS questionnaires.

All study data collection was completed in a single patient visit, which was conducted at a regular patient visit to the physician/investigator in the context of his/hers standard monitoring plan.

Selection Criteria

Inclusion Criteria

Patients should meet the following criteria in order to participate in the study:

1. Provision of written informed consent.
2. Patients aged ≥ 18.
3. Patients with upper-GI symptoms the last week prior to the study visit.

Exclusion Criteria

Any of the following were considered as a criterion for exclusion from study:

1. History of oesophageal, gastric or duodenal surgery.
2. Patients with history of malignancy.
3. Treatment with acetylsalicylic acid/NSAID during the last week prior to the study visit.
4. Therapy with PPI for the healing of ulcer induced by treatment with acetylsalicylic acid/NSAID.
5. Therapy with PPI for HP eradication or for healing of HP-related peptic ulcer.

Target patient Population, Study Disease and Sample Size

Patient population included patients with upper GI tract symptoms during the last week prior to the study centre visit.

Sample size calculation was based on study's primary endpoint, which is the determination of the prevalence of GERD in a representative sample of patients among the Greek population who visit hospital based physicians in regional areas complaining of upper gastrointestinal (GI) symptoms. According to recently published bibliographic data of an epidemiological study conducted in a representative sample of the general

population of Greece, GERD prevalence in patients with upper and lower GI tract symptoms has been estimated to be 65%. Therefore, considering that in the present study the expected proportion of those with GERD is estimated to be 65% the assessment of 546 subjects was required in order to detect GERD prevalence of 0.65 in the population with power 85%, precision of approximately plus/minus 0.04 points (95% confidence interval: ± 4%), significance level a=0.05 and two-tailed test (Relative Standard Error: 3.14%). Thus, an observed proportion of 0.65 would be reported with a 95% confidence interval (CI) ranging from 0.61 to 0.69. Withdrawal rate has not been taken into account since according to the study design only one visit is planned to be performed for the collection of the required epidemiological data. However, taking into account that approximately 9% of patients would not provide evaluable data for various reasons such as missing data, protocol violations etc, approximately 600 patients were finally required in order to ensure the aforementioned sample size for the final statistical analysis.

The sample size determination was performed using the statistical package Sample Power 2.0 - SPSS.

Statistical Methods

Descriptive statistical analysis was performed for all study data and epidemiological methods were applied for the process and presentation of results. Continuous variables were summarized with the use of descriptive statistical measures [mean value, standard deviation (SD), median, first and third quartiles and extreme values]. Categorical/distinct variables were displayed as frequency tables (N, %). Furthermore, the impact of prognostic factors on the change of the outcome variables will be evaluated with the use of linear regression models for the continuous outcome variables, and using logistic regression models for the distinct outcome variables, respectively. All the above mentioned statistical tests were two-sided and were performed at a 0.05 significance level. The interpretation of all results was performed in a descriptive manner and missing data were not replaced.

RESULTS:

Descriptive Analysis

Tables 2a – 2e present demographic and basic epidemiological and clinical characteristics of the study patients.

Table 2a. Demographic characteristics of the study population

Demographic characteristics	
Gender n, (%)	
Males	258 (43.0)
Females	342 (57.0)
Height (cm) (mean ± SD)	169.1 ± 9.85
Weight (kg) (mean ± SD)	77.4 ± 14.7
Family Status (n, %)	
Single	117 (19.5)
Married	427 (71.2)
Divorced	22 (3.7)
Widower	34 (5.7)
Educational status (n, %)	
Illiterate	31 (5.2)
Primary	171 (28.5)
Secondary	191 (31.8)
Tertiary	207 (34.5)
Employment (n, %)	
Employed	322 (53.7)
Unemployed	23 (3.8)
Pensioner	156 (26.0)
Housekeeping	84 (14.0)
Student	13 (2.2)
Other	2 (0.3)
Place of stay (n, %)	
Urban	312 (52.0)
Suburban	153 (25.5)
Rural	135 (22.5)

Table 2b. Smoking history, alcohol consumption, prior dietary advice

	n (%)
Smoking history	
Non smoker	329 (54.8)
Occasional smoker	40 (6.7)
Quit	85 (14.2)
Current Smoker	146 (24.3)
Number of cigarettes per day (mean ± SD)	23.8 ± 13.8
Number of years smoking (mean ± SD)	21.4 ± 12.0
Number pack years (mean ± SD)	27.4 ± 25.4
Quit smoking (n, %)	
< 1 year	17 (20.0)
> 1 year	68 (80.0)
Alcohol consumption (n, %)	
Non	304 (50.7)
Low (<1 glass/day)	181 (30.2)
Moderate (1-2 glasses/day)	90 (15.0)
High (>3 glasses/day)	25 (4.2)
Dietary advice (n, %)	
No	335 (55.8)
Yes	265 (44.2)

Table 2c. Upper GI tract history and treatment

	n (%)
Upper gastrointestinal tract history	
No	279 (46.5)
Yes	321 (53.5)
Treatment of upper GI tract symptoms	
No	372 (62.0)
Yes	228 (38.0)
Frequency of administration	
On demand	148 (64.9)
Continuous	80 (35.1)

Table 2d. General medical history

Significant chronic diseases other than GI disorders	n	%
No	289	48.1
Yes	311	51.6
Cardiovascular disease	159	51.1
Endocrine disorders	88	28.3
Metabolic and nutritional disorders	60	19.3
Musculoskeletal and connective tissue disorders	44	14.1
Respiratory system, thoracic and mediastinal disorders	42	13.5
Hepatobiliary disorders	31	10.0
Psychiatric disorders	26	8.4
Eye disorders	25	8.0
Renal and urinary disorders	22	7.1
Neurological disease	18	5.8
Ear and labyrinth disorders	14	4.5
Urogenital disorders	9	2.9
Blood and lymphatic system disorders	7	2.2
Reproductive system and breast disorders	6	1.9
Immune system disorders	4	1.3
Skin and subcutaneous tissue disorders	2	0.6
Infections and infestations	1	0.3
Other	15	4.8

Table 2e. Upper GI tract medical history (n=319)

	n	%
GERD	181	56.7
Esophagitis	62	19.4
Hiatus hernia	39	12.2
Gastric ulcer	23	7.2
Duodenal ulcer	33	10.3
Gastritis/Duodenitis	84	26.3
Other	22	6.9
Dyspepsia	2	0.006
Epigastric pain	3	0.009
Irritable bowel	2	0.006
Heartburn	2	0.006
Bile colic	2	0.006
Flatulence	1	0.003
Gastric neurosis	1	0.003
Cholocystitis	4	0.013
Acid belching	1	0.003
Pancreatitis	1	0.003
Gastric disorders	1	0.003
Bloating	1	0.003
Cholelithiasis	2	0.006

Primary Objective

Prevalence of GERD was assessed with the use of the GerdQ questionnaire. Patients with a total GerdQ score ≥ 8 were considered as having GERD, whereas those with a score of 0-7 were considered as having a low probability of GERD. Overall, 67.5% of the study population was considered as suffering from GERD (table 3a).

Table 3a. GERD prevalence based on GerdQ questionnaire (n=600)

	n	%
GERD via GerdQ		
No	195	32.5
Yes	405	67.5

Secondary Objectives

GERD prevalence as assessed on the basis of reported symptoms

Prevalence of GERD was also assessed on the basis of reported symptoms and taking as a cut-off point a frequency of ≥2 days/week for heartburn and/or regurgitation. According to this, it was estimated that 69.3% of the study population was suffering from GERD at the time of the study visit (table 4).

Table 4. GERD prevalence according to reported upper GI tract symptoms

	n	%
GERD symptoms		
No	184	30.7
Yes	416	69.3

Antisecretory treatment

Table 5a. Number of patients who were receiving antisecretory treatment for upper GI tract disorders at the time of the study visit

	n	%
No	372	62.0
Yes	228	38.0

From the 228 patients who received antisecretory treatment, 81 (35.5%) followed a continuous administration. Their compliance to treatment is shown in Table 5b.

Table 5b. Patients' compliance to antisecretory treatment (frequency of missed doses)

Missed doses	n	%
>1 time per week	9	11.1
1 per week	8	9.9
1 every 2 weeks	4	4.9
≤1 time per month	2	2.5
Takes all doses	58	71.6

Percentage of GERD patients that may require modification of their antisecretory treatment (response to treatment)

The percentage of patients in need of treatment change was estimated via the positive predictive factors for GERD of GerdQ questionnaire (A1, A2 & C5, C6), in the population that reported to take antisecretory treatment (continuous or as needed, n=228 Table 5a) at the time of the study visit. Specifically, patients who reported heartburn or regurgitation or sleep disturbance or additional OTC treatment receipt for heartburn/regurgitation at a frequency of ≥2 times per week, were considered as in need of treatment change (table 6a).

Table 6a. Percentage of patients who may require antisecretory treatment change

	n	%
Treatment change need		
No	45	19.7
Yes	183	80.3

Prevalence and severity of extraesophageal symptoms

Extraesophageal symptoms were recorded with the XQS questionnaire. XQS questionnaire is an exploratory tool, designed to evaluate the frequency and severity of extraesophageal symptoms, based on a 6 grade Likert scale (0-5), where the higher the score the more severe and more frequent the symptoms are. The prevalence and severity of extraesophageal symptoms in the study populations are listed in tables 7a and 7b respectively.

Table 7a. Prevalence of extraesophageal symptoms via XQS questionnaire

	n (%)					
	0	**1**	**2**	**3**	**4**	**5**
Sleep disturbance	242 (40.3)	100 (16.7)	114 (19.0)	86 (14.3)	13 (2.7)	45 (7.5)
Chest pain	358 (59.7)	82 (13.7)	70 (11.7)	44 (7.3)	20 (3.3)	26 (4.3)
Daytime cough	393 (65.5)	71 (11.8)	66 (11.0)	31 (5.7)	12 (2.0)	27 (4.5)
Night time cough	390 (65.0)	75 (12.5)	67 (11.2)	39 (6.5)	13 (2.2)	16 (2.7)
Hoarseness	443 (73.8)	60 (10.0)	55 (9.2)	19 (3.2)	6 (1.0)	17 (2.8)
Wheezing	479 (79.83)	61 (10.2)	36 (6.0)	11 (1.8)	3 (0.5)	10 (1.7)
Difficulty swallowing food	431 (71.8)	63 (10.5)	60 (10.0)	28 (4.7)	6 (1.0)	12 (2.0)
Nausea	336 (56.0)	74 (12.3)	69 (11.5)	70 (11.7)	17 (2.8)	34 (5.7)

0 = never, 1 = 1 day, 2 = 2 days, 3 = 3-4 days, 4 = 5-6, 5 = everyday.

Table 7b. Intensity of extraesophageal symptoms via XQS questionnaire

	n (%)					
	0	**1**	**2**	**3**	**4**	**5**
Sleeping disturbance	243 (40.6)	33 (5.5)	124 (20.7)	126 (21.0)	54 (9.0)	19 (3.2)
Chest pain	356 (59.3)	49 (8.2)	75 (12.5)	73 (12.2)	32 (5.3)	15 (2.5)
Daytime cough	393 (65.5)	56 (9.3)	74 (12.3)	58 (9.7)	14 (2.3)	5 (0.8)
Nighttime cough	390 (65.0)	57 (9.5)	69 (11.5)	67 (11.2)	12 (2.0)	5 (0.8)
Hoarseness	442 (73.7)	53 (8.8)	61 (10.2)	30 (5.0)	13 (2.2)	1 (0.2)
Wheezing	478 (79.7)	48 (8.0)	40 (6.7)	25 (4.2)	8 (1.3)	1 (0.2)
Difficulty swallowing food	430 (71.8)	50 (8.4)	62 (10.4)	41 (6.8)	13 (2.2)	3 (0.5)
Nausea	337 (56.2)	45 (7.5)	68 (11.3)	70 (11.7)	55 (9.2)	25 (4.2)

0 = none, 1 = very mild, 2 = mild, 3 = moderate, 4 = moderate/severe, 5 = severe.

Extraesophageal symptoms and possibility of GERD

The possibility of a patient to present with GERD based on extraesophageal symptoms recorded via the XQS questionnaire was investigated via the odds ratios (OR) analysis. Table 9, presents average changes in OR (95% CI), per unit change in the XQS (approximate measure) in GERD prevalence, as estimated by the GerdQ questionnaire.

Table 8: OR for positive Gerd calculated for unit change of extraesophageal symptoms

Symptoms	**OR**	**95% CI**	**p-value**
Sleep disturbance	2.04	1.73 – 2.41	<.0001
Chest pain	1.32	1.14 – 1.52	0.0001
Daytime cough	1.18	1.02 – 1.35	0.023
Night time cough	1.62	1.34 – 1.96	<.0001
Hoarseness	1.42	1.17 – 1.73	0.0004
Wheezing	1.49	1.15 – 1.92	0.002
Difficulty swallowing food	1.34	1.12 – 1.62	0.002
Nausea	0.84	0.76 – 0.94	0.002

OR: odds ratio, CI: confidence interval.

We further investigated the correlations between GERD prevalence, and extraesophageal symptoms as recorded via the XQS questionnaire. Using logistic regression it was observed that sleep disturbance ($p<0.0001$), chest pain ($p<0.0001$), daytime cough ($p=0.02$), night time cough ($p<0.0001$), hoarseness ($p=0.0004$), wheezing ($p=0.002$) and difficulty swallowing ($p=0.002$) are positively related with GERD prevalence, while nausea is negatively related ($p=0.002$) (table 9).

Table 9. Pearson's correlation coefficient (r) between extraesophageal symptoms and GERD

	Extraesophageal symptoms (XQS)							
	Sleep disorder	**Chest pain**	**Cough (daytime)**	**Cough (nighttime)**	**Hoarseness**	**Wheezing**	**Difficulty swallowing**	**Nausea**
r	0.45	0.16	0.08	0.25	0.12	0.14	0.12	-0.23