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Cost effectiveness of the fixed combination of indacaterol / glycopyrronium versus salmeterol / fluticasone and tiotropium in the management of patients with COPD in Greece

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ABSTRACT

Background: This study aimed at estimating the cost-effectiveness of the fixed-dose combination indacaterol/glycopyrronium (IND/GLY) 85/43μg versus salmeterol/ fluticasone 50/500μg (SFC) and tiotropium 18μg (TIO) in the management of patients with chronic obstructive pulmonary disease (COPD) in Greece.

Methods: A microsimulation model was developed in MS Excel. Effectiveness and utility data were obtained from the international literature and mortality data from the WHO database. Distribution of patients by severity stage of airflow limitation, maintenance costs and costs associated with severe/ non-severe exacerbations were taken from published Greek studies. Unit costs were taken from officially published sources (Price Bulletin, reimbursement list, diagnosis-related groups). The study perspective was that of the Social Insurance Fund; costs and outcomes were discounted at 3.5%, and the outcomes are reported over time horizons of one, three, five and 10 years and over a lifetime. Deterministic and probabilistic sensitivity analyses were conducted to test robustness of model results.

Results: Treatment of COPD with IND/GLY is associated with increased efficacy both versus SFC (additional life years -LYs: 0.19; additional quality adjusted life-years -QALYs: 0.13) and TIO (additional LYs: 0.22; QALYs: 0.16). Although IND/GLY has a higher pharmaceutical cost (additional €2,626 vs. SFC; additional €2,679 vs. TIO), all other cost components (maintenance costs, severe and non-severe exacerbation costs) are reduced, resulting in a reduction of total costs by €5,204 compared with SCF and €7,126 compared with TIO.

Conclusions: IND/GLY was found to be a dominant treatment strategy compared to SFC and TIO for the management of patients with COPD in Greece, which could lead to savings for the healthcare system.

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a life-threatening, debilitating lung disease that severely impacts normal breathing and daily activities [1]. In 2012, more than 3 million people worldwide lost their lives due to COPD, accounting for 6% of all deaths globally for that year [1].

COPD is a major cause of morbidity and mortality, with a significant cost and societal burden, especially in the developed countries [2–6]. Its significant economic burden on individuals and society originates from difficulties associated with correct diagnosis, its chronic nature, the acute worsening or COPD exacerbations, and the indirect costs associated with reduced ability to work [2–6].

The direct and indirect costs associated with the disease exhibit an increasing trend and vary significantly across countries [7]. In Greece, the disease prevalence in the population above the age of 35, with a smoking history of >100 cigarettes per lifetime, has been estimated at 8.4% [8], while the average cost of managing a COPD exacerbation is estimated at €1,711 [9].

The fixed combination of indacaterol/glycopyrronium 85/43µg (IND/GLY) is a once-daily inhaled combination of indacaterol maleate, a long-acting 2-adrenergic agonist (LABA), and glycopyrronium bromide, a long-acting muscarinic antagonist (LAMA). It is indicated by the European Medicines Agency (EMA, October 2013) as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD [10].

A recently published systematic review showed that IND/GLY provides significant and clinically meaningful improvements on several important COPD outcomes. Relevant studies have demonstrated that therapy with IND/GLY is superior to therapy with a single long acting bronchodilator, even in patients who report symptoms despite being under treatment [11].

The purpose of this study was to compare the costs and outcomes of IND/GLY versus salmeterol/fluticasone 50/500µg (SFC) and tiotropium 18µg (TIO) in the management of patients with COPD in Greece.

METHODS

Model design

For the economic evaluation of IND/GLY versus SFC and TIO, a patient simulation model was developed in Excel 2010®, described in detail by Price et al [12]. The model time horizon varied across one, three, five and 10 years and over a lifetime; costs and outcomes were discounted at 3.5% annually [13,14]. The perspective of the analysis was that of the Social Insurance Fund (SIF), thus only direct medical costs reimbursed by the SIFs in Greece were taken into consideration. All costs are in 2014 Euros.

MODEL INPUTS

Clinical data

Effectiveness data used in the model were based on the results of three phase III randomized controlled trials: SHINE [15], SPARK [16] and ILLUMINATE [17]. In particular, inputs for IND/GLY versus SFC were based on ILLUMINATE [17], using the TORCH study [18,19] to calibrate against a placebo baseline. Inputs for IND/GLY versus TIO were based on of the results of SHINE [15] and SPARK studies [16].

Population and mortality data

Population data categorized by age and sex for Greece were taken from the Organization for Economic Cooperation and Development (OECD) Population Statistics 2012 (http://stats.oecd.org/). All-cause mortality data (life-expectancy, central death rates, the probability of dying and number of survivors by age group) were obtained from the World Health Organization (WHO life-tables for Greece 2012 (http://www.who.int/gho/mortality_burden_disease/life_tables/en/). Due to lack of Greek data on COPD-specific mortality, the hazard ratio was based on the study by Lindberg and colleagues [20].

Patient demographic characteristics (mean age entering the model and percentage of males versus females), as well as patient distribution according to airflow limitation as defined by the 2010 global initiative for chronic obstructive pulmonary disease (GOLD) classification [21] and mean FEV1% by GOLD stage were taken from studies in the Greek COPD population and are presented in Table 1.

COST DATA

For pharmaceutical costs, retail prices were taken into consideration (published in the Price Bulletin of the Ministry of Health and Social Welfare [23]), after subtracting patient co-payment (Table 2).

The costs associated with the management of severe and non-severe exacerbations were based on studies conducted on the Greek COPD population (Table 3). Severe exacerbations were defined as exacerbations requiring hospitalization. For severe exacerbations, the mean actual cost per exacerbation requiring hospitalization across all stages of the disease was taken into consideration. Both costs of severe and non-severe exacerbations were subsequently inflated with the Health Price Index (HPI) to reflect 2014 prices.

Maintenance costs included maintenance medication and non-medication costs (patient follow-up and lab tests), that do not relate to the management of exacerbations, after excluding pharmaceutical costs of the interventions compared (Table 4). Based on Greek leading experts' opinion, maintenance costs for GOLD stages I and II were negligible and thus excluded from the analysis. Costs for GOLD stages III and IV were based on published data by Geitona and colleagues [25]. The study estimated the cost of moderate-to-severe patients. This cost was broken down to moderate and severe patients based on the distribution of respective costs in the Swedish study by Price and colleagues [12] and was inflated with the HPI to reflect 2014 prices.

UTILITY DATA

Utility data were obtained from the Rutten-van Molken et al. study [26] and are presented in Table 5.

Table 1.
Patient demographic characteristics, distribution & mean FEV1% by 2010 GOLD stage

	Mean (s.d.)	Source
Age entering the model (years)	67.6 (10.2)	Papaioannou et al., 2014 [22]
% of males	71.3%	Papaioannou et al., 2014 [22]
Patient distribution by GOLD stage		Papaioannou et al., 2014 [22]
GOLD I	19.32%	
GOLD II	35.44%	
GOLD III	25.63%	
GOLD IV	19.61%	
Mean FEV1% by GOLD stage		Geitona et al., 2011 [9]
GOLD I	83.0% (5.2%)	
GOLD II	62.7% (11.3%)	
GOLD III	52.3% (16.5%)	
GOLD IV	38.8% (11.7%)	

Table 2.
Pharmaceutical costs

Drug	Cost per package (€)	Number of units per package	Cost per unit (€)	Number of units per day	Daily drug cost (€)
IND/GLY	53.20	30	1.77	1	1.77
SFC	29.99	60	0.50	2	1.00
TIO	29.63	30	0.99	1	0.99

Table 3.
Exacerbation costs

	Cost per occurrence (€)	Source
Non-severe exacerbation	572	Sonathi et al 2014 [24]
Severe exacerbation	1,839	Geitona et al. 2011 [9]

Table 4.
Annual maintenance costs

	Cost (€)	Source
GOLD I	-	
GOLD II	-	
GOLD III	3,205	Geitona et al. 2011 [25]
GOLD IV	10,72	Geitona et al. 2011 [25]

Table 5.
Utility values

Variables	EQ-5D Utility Score
Constant	0.688
Gender (male vs. female)	+0.057
Postbroncodilator therapy FEV1 % predicted	+0.003
BMI	-0.003
Number of concomitant diseases in the previous year	-0.01
Number of emergency department visits not resulting in hospital admission in the previous year	-0.029
Number of hospital admissions in the previous year	-0.02

Sensitivity analysis

Deterministic and probabilistic sensitivity analyses were performed in order to investigate uncertainty around model results. The model inputs that were varied by +/-20% in the one-way sensitivity analysis were FEV1% improvement, exacerbation rate versus placebo, and disease severity of population (distribution of patients according to GOLD airflow limitation classification) at baseline. This range reflects habitually used ranges in the literature for one-way sensitivity analysis [27,28]. The probabilistic sensitivity analysis (PSA) was conducted for 1000 cohorts with 10,000 patients per cohort. The purpose of the PSA was to examine the effects of variability of effectiveness and cost data on the incremental cost-effectiveness ratio (ICER). Gamma distributions. The output of the PSA is presented in scatterplots of 1000 simulated ICERs on the cost-effectiveness plane.Source: Rutten-van Molken et al., 2006 [26]

RESULTS

Total per patient costs of managing COPD patients with IND/GLY over lifetime were estimated at €45,459 (Table 6). The respective costs for SFC and TIO were estimated at €50,663 and €52,585. Maintenance costs constitute the largest cost component, accounting for 81.9%%, 88% and 87.4% of total costs for treatment with IND/GLY, SFC and TIO, respectively.

Treatment with IND/GLY is associated with cost savings compared with both SFC and TIO from the 1st year of treatment and over three, five and 10 years, as well as over lifetime (Table 7).

Table 6.
Cost-effectiveness of IND/GLY versus SFC and TIO

	IND/GLY	SFC	TIO	Difference vs. SFC	Difference vs. TIO
LYs	9.87	9.68	9.649	0.19	0.22
QALYs	5.96	5.83	5.8	0.13	0.16
Total cost (€)	45,459	50,663	52,585	-5,204	-7,126
Drug cost (€)	5,859	3,233	3,181	2,626	2,679
Maintenance cost (€)	37,219	44,558	45,98	-7,339	-8,76
Exacerbation costs (€)	2,381	2,872	3,425	-491	-1,044

Table 7.
Incremental results of the base case cost-effectiveness analysis for IND/GLY versus SFC and TIO

Time horizon	1 year	3 years	5 years	10 years	Lifetime
IND/GLY vs. SFC					
Incremental total costs (€)	-453	-1,813	-2,997	-4,949	-5,204
Incremental LYs	0.00	0.01	0.02	0.08	0.19
Incremental QALYs	0.00	0.01	0.02	0.06	0.13
Exacerbations avoided	0.06	0.22	0.35	0.63	0.92
IND/GLY vs. TIO					
Incremental total costs (€)	-692	-2,624	-4,315	-6,988	-7,126
Incremental LYs	0.00	0.01	0.03	0.10	0.22

Overall, the analysis showed that IND/GLY is associated with increased effectiveness compared with SFC, both in terms of life-years (LYs) gained (0.19) and quality-adjusted life years (QALYs) gained (0.13). Similarly, treatment with IND/GLY is associated with more LYs (0.22) and QALYs (0.16) versus TIO.

Treatment with IND/GLY is also associated with a lower total cost compared with both SFC and TIO. In particular, although IND/GLY has a greater drug cost than SFC and TIO, this is completely offset by a reduced cost in maintenance treatment and management of (severe and non-severe) exacerbations (Table 6). The combination of increased effectiveness and reduced costs render IND/GLY a dominant treatment strategy versus SFC and TIO in the management of patients with COPD in Greece.

Sensitivity analyses results

Results of the one-way sensitivity analysis suggested that the parameters which had the most significant impact on the results were FEV1% improvement and the disease severity of the patients included in the analysis. The results of the PSA are presented in a cost-effectiveness plane of IND/GLY versus SFC and TIO in Figures 1 and 2, respectively. The PSA confirmed robustness of model results, as it showed that IND/GLY was dominant in the majority of iterations. The probability of being cost effective at a threshold of €30,000 per QALY gained was 99.9% and 97.1% versus SFC and TIO, respectively.

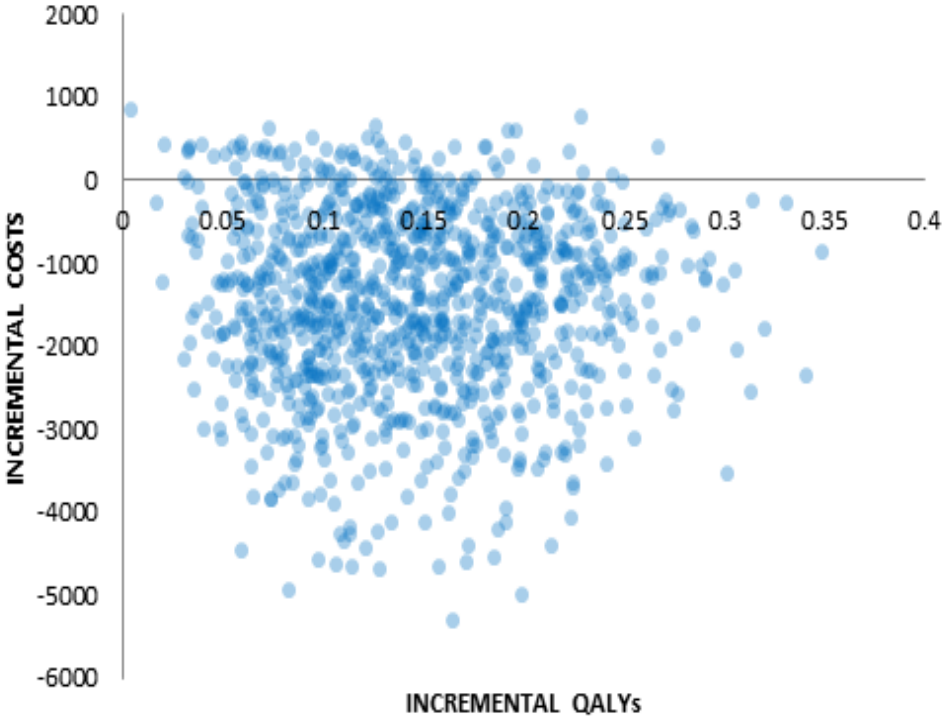

Figure 1.
Cost-effectiveness plane for IND/GLY versus SFC based on PSA

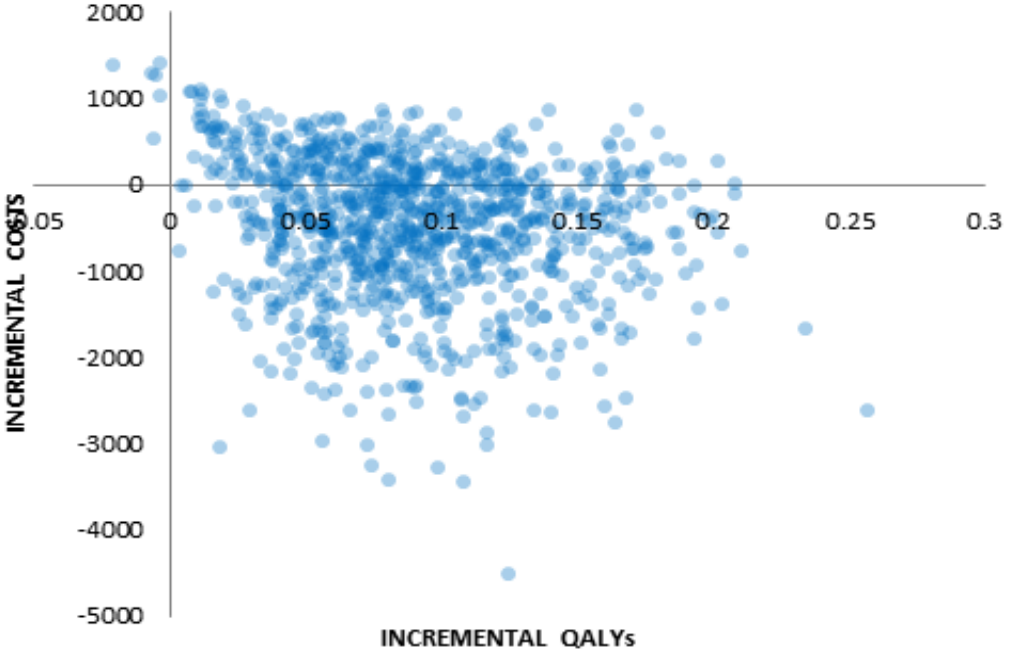

Figure 2.
Cost-effectiveness plane for IND/GLY versus TIO based on PSA

DISCUSSION

The results of the cost-effectiveness analysis showed that IND/GLY was associated with cost savings, and efficacy and safety benefits when compared with SFC and TIO, thus was found to dominate alternative treatments. In particular, the present study suggests that IND/GLY was associated with incremental cost savings at all time-horizons at a daily cost of €1.77.

The results of this analysis are comparable to results of the economic evaluation study of IND/GLY in Sweden. In particular, the study by Price and colleagues, suggested that IND/GLY is cost-minimising versus the free combination of indacaterol and glycopyrronium (IND+GLY) and dominates SFC in the maintenance treatment of COPD patients in Sweden [12]. In addition, previously conducted research on the costs of COPD treatments in the Greek health care setting has estimated the mean annual per patient cost of tiotropium at €2,504 [29], which is comparable to current results.

The present analysis had the following limitations. Mean FEV1% values by GOLD stage were taken from the study by Geitona and colleagues [9], which referred to a patient population with more severe disease (patients hospitalized due to COPD). This is of particular importance since disease severity is one of the key parameters impacting results. However, inputs on disease severity were tested in the sensitivity analysis and confirmed that even when only moderate patients were considered in the model, IND/GLY remained a cost-effective treatment strategy.

Another limitation of this study is that indirect costs were not included in the analysis. A Swedish study showed that annual indirect costs increased with disease severity, ranging from SEK 3,133 to SEK 118,517 for GOLD I to GOLD IV stages, respectively [30]. The inclusion of indirect costs into our study would have provided a more complete picture of the true costs of COPD in Greece. However, the perspective of the present study was that of the SIFs, thus the study focused only on direct medical costs associated with disease management.

In Greece, pharmacoeconomic studies are currently not officially requested by Reimbursement Authorities. However, taking them into consideration could serve as an evidence basis for rational decision making and improvement of resource allocation. To the best of our knowledge this study is the first to evaluate the use of IND/GLY and the associated costs in the local treatment pathway and thus could help inform health care decision making.

CONCLUSIONS

This study suggests that IND/GLY is more effective (increases both LYs and QALYs) and less costly for Social Insurance Funds versus both SFC and TIO. Thus, IND/GLY is a dominant treatment strategy in the management of patients with COPD in Greece and could lead to savings for the health care system. The results of this study could support informed health care decision making and contribute to a more rational allocation of health resources.

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