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ORIGINAL RESEARCH

Real-life cost and cost-effectiveness for tiotropium 18 µg od monotherapy in moderate and severe COPD patients: a 48-month survey

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ABSTRACT

BACKGROUND: Tiotropium monotherapy enables a significant minimization of morbidity in COPD. OBJECTIVE: to evaluate and compare cost and cost-effectiveness of tiotropium monotherapy administrated for 24 months (18 µg od) in mild-to-moderate and severe chronic obstructive pulmonary disease (COPD). METHODS: Clinical outcomes (days in hospital; visits in general ward; cycles of systemic steroids; cycles of antibiotics and maintenance therapy drugs) were evaluated in two groups of patients corresponding to predicted FEV1 baseline values ≤ 50% (A) and > 50% (B) from the Italian NHS perspective. In order to perform cost-effectiveness analysis, FEV1 value, available for each patient, was converted in SGRQ score using a published multivariate linear model. Utilities were then obtained through the Ståhl equation. RESULTS: The comparison between 24 months of standard therapy and subsequent 24-month period of tiotropium monotherapy showed that hospitalization cost, which represents the driving treatment cost, drops from 77% to 69% (A) and from 67% to 33% (B) of the total cost. Differently, maintenance therapy cost increased but the amount was more than offset by the savings accruing from the shortening of hospitalization. Furthermore, cost-effectiveness results revealed a mean savings of about 216 € (A) and 961 € (B) other than a mean gain of 0.07 QALY (A) and 0.02 QALY (B). Dominance of tiotropium (calculated only within patients completing treatment course) revealed that in almost 29% (A) and 36% (B) of subjects tiotropium strategy is dominant while only in 2% (A) and 7% (B) of cases is associated to costs increment and worsening on quality of life. The dominance was systematic in severe COPD. Statistical analyses confirm such trend. CONCLUSIONS: Results of the present study suggest that tiotropium used as unique treatment in COPD systematically consents significant costs savings together with positive effects on evaluated quality. These effects prove proportional to COPD severity.

Keywords

COPD; Cost-effectiveness; Tiotropium

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) represents a pathological condition of the respiratory system which maximally prevails since the 5th decade of life: it is only partially reversible, and can progressively affect both lung structures and function. COPD is one of the most common causes of morbidity and mortality worldwide, and it is characterized by a very high socio-economic impact, particularly for health systems of industrialized countries [1-3].

The governance of the disease is based on a complex strategy, such as: stopping smoking; symptom control; improvement in respiratory function; reduction in exacerbation rate; improvement in quality of life; healthcare cost control. All these outcomes should be checked over a long-term period in order to assess their absolute value both in clinical and economic terms.

Despite the wide consensus concerning COPD as a progressive disease, the convenience of therapy has been mainly focused in the most severe stages of COPD (GOLD stages 3 and 4), while the hypothesis that current therapeutic options might also be effective in earlier stages of COPD and might

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be able to influence the disease progression was almost completely neglected up to a recent past. Actually, the hypothesis that also the earlier treatment of COPD might be useful and convenient was accepted only after the suggestions emerged from the two most important international long-term clinical trials published in the last years [3,4], and particularly after the *post-hoc* and secondary analyses carried out within these large studies [5-9].

A recent observational study compared the effects of current therapeutic options with tiotropium bromide monotherapy administrated for 24 months (18 µg od) in patients suffering from mild-to-moderate and severe COPD [10]. The study showed that tiotropium monotherapy enables a significant minimization of morbidity in two groups of COPD patients corresponding to predicted FEV1 baseline values ≤ 50% and > 50%m respectively [10]. Data collected in this study were used with the aim of performing and comparing cost and cost-effectiveness analyses for tiotropium monotherapy (18 µg od) administrated over a 24-month period in patients suffering from mild-to-moderate and severe chronic obstructive pulmonary disease (COPD) from the Italian National Health System (NHS) perspective.

Outcomes	Cost (€)	Notes
Hospital stay		
ICU stay	3,565	DRG 565
Chronic/acute RF	3,565	DRG 87
COPD exacerbation	2,424	DRG 88
GP visit	16.60	One GP visit
Systemic steroids	12.43	One cycle of systemic steroids
Antibiotics	62.57	One cycle of antibiotics
Maintenance therapy		
First 24 months of analysis	449.82	Annual main therapy (ICS+LABA, LAMA, MTX)
Subsequent 24 months	620.78	Annual tiotropium monotherapy

Table I. *Unit cost of clinical outcomes exploited in the analyses*
GP: general practitioner, ICS: inhaled corticosteroids, LABA: long-acting beta-agonists, LAMA: long-acting muscarinic antagonists, MTX: methylxanthines; RF: respiratory failure

METHODS

Dataset used in the analysis was automatically extracted from the central Database according to the procedure already analytically described in a previous paper [10]. The division of subjects into two groups according to their FEV1 basal value > or > 50% predicted was maintained.

All subjects were followed for 4 years: the outcomes of the 24 months of current therapy (CT) preceding the index date were compared to those obtained with regular monotherapy tiotropium 18 µg daily (MT) for the subsequent two years.

Economic value of clinical outcomes are reported in Table I.

Hospital cost was evaluated as the mean cost of ICU and hospital admissions for COPD exacerbation and chronic/acute respiratory

Antibiotics	Package	Unit cost (€)	Packages per cycle (n°)	Cost per Cycle (€)		Composition (%)
Ceftazidime	1 g powder for solution for injection,10 vials	48.31	3	144.92	154.75	25
	1 g/3ml monovial	5.49	30	164.59		
Moxifloxacin	400 mg 5 film-coated tablets	20.86	2	41.71		20
Ciprofloxacin	500 mg 6 film-coated tablets	6.54	4	26.14		20
Amoxifloxacin+ clavulanic acid	875 mg + 125 mg 12 film-coated tablets	9.82	3	29.45	29.45	35
	875 mg + 125 mg powder for oral suspension, 12 sachets	9.82	3	29.45		
Mean cost for one cycle of antibiotics (€)				62.57		

Table II. *Detailed composition of one cycle of antibiotics*

Drugs	Cost per package (€)	Packages per year (n°)	Therapy composition (%)	
			CT	TM
Fluticasone/ salmeterol	68.79	6	30	-
Budesonide/ formoterol	59.51	12	35	-
Beclomethasone/ formoterol	49.22	4	3	-
Theo-dur	3.14	24	20	-
Tiotropium	47.75	13	9	100
Mean cost for one year of maintenance therapy (€)			**449.82**	**620.78**

Table III. *Detailed composition of maintenance therapy prior to tiotropium monotherapy*

failure (RF) [11] weighted for the frequency reported for each year. Visits to general practitioner (GP) was taken from Garattini et al. [12] and actualized to 2013 [13]. Drugs consumption (maintenance and exacerbation management drugs) was measured and valued [14] in terms of prescribed packages, furthermore discount applied by pharmacies was considered in the cost evaluation. Cost for one cycle of antibiotics and yearly maintenance therapy cost (both for CT and MT) are detailed in Table II and Table III. FEV1 values, available at several time points for each patient, were converted in SGRQ scores using a published multivariate linear model [15], then utilities were obtained through the Ståhl equation [16].

Difference between CT and MT in both groups were tested using Welch test (for continuous variables) and chi-squared test (for dichotomous variables). All analyses were performed using the statistical software R. Also the cost-effectiveness of tiotropium monotherapy was inferred from the sample analysis [17] and presented in terms of confidence ellipses and probabilistic cost-effectiveness acceptability curves (CEAC).

	Year 1	Year 2	Year 3	Year 4
Group A (FEV1≤50%)				
N patients	154	142	133	129
Unitary costs (€)				
• Hospital stays	1,664.81	2,035.04	1,700.21	1,371.55
• GP visits	20.26	17.88	12.48	16.21
• Steroids	3.79	3.50	2.80	2.89
• Antibiotics	107.67	84.60	71.98	61.60
• Maintenance therapy	449.82	449.82	620.78	620.78
Total cost (€)	**2,246.35**	**2,590.84**	**2,408.25**	**2,073.03**
Group B (FEV1>50%)				
N patients	165	159	140	126
Unitary costs (€)				
• Hospital stays	705.10	1,189.02	309.42	327.02
• GP visits	10.86	8.39	4.36	5.40
• Steroids	1.73	1.95	2.03	3.35
• Antibiotics	8.72	26.37	22.63	18.37
• Maintenance therapy	449.82	449.82	620.78	620.78
Total cost (€)	**1,176.23**	**1,676.55**	**959.21**	**974.92**

Table IV. *Annual management cost per COPD patient resulted from the cost analysis*

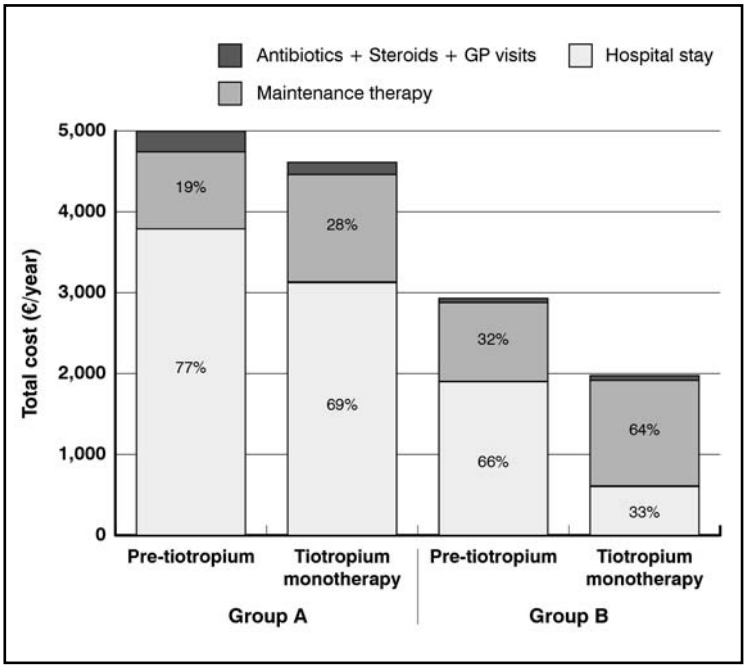

Figure 1. *Detailed costs for group A and group B patients: comparison between current therapy and tiotropium monotherapy*

RESULTS

The whole sample consisted of 319 COPD subjects: Group A (154 severe COPD patients; 104 males, mean ± SEM age = 72.1 ± 0.51 years; FEV1% pred. = 45.4 ± 0.61; FVC % pred. = 63.6 ± 0.48), and group B (165 mild-to-moderate COPD patients, 111 males, mean ± SEM age = 71.4 ± 0.60 years; FEV1 % pred. = 65.5. ± 5.7 ; FVC % pred. = 64.7 ± 0.85. The two groups proved homogeneous in terms of distribution by gender, age, and use of systemic steroids; they were obviously significantly different only in terms of basal lung function, and of morbidity of the disease [10].

Total cost per patient per year is detailed in Table IV. Results from comparison between 24 months of CT and subsequent 24 months of MT showed that hospitalization cost, which represents the main cost driver, dropped from 77% to 69% (A), and from 66% to 33% (B), of the total cost, (Figure 1). Conversely, maintenance therapy cost increased but this amount was more than offset by the savings accruing from the shortening of hospitalization (Figure 1). The re-distribution of cost composition resulted statistical significant in both groups: p=0.03 (A), p<0.0001 (B).

Furthermore, cost-effectiveness results (Table V) revealed a mean savings of more than 216 € (p=0.63) in the Group A, and 961 € (p<0.0001) in the Group B, alongside a mean gain of 0.07 (p<0.001), and 0.02 QALY (p=0.53), respectively. One-side Welch test performed on non-significant results estimate that total cost per patients of MT can exceed CT at most of 516 € (A) while the loss of QALY is not greater than 0.03 (B), p<0.05 for both analyses.

	24 months CT	24 months MT	Difference	p-value
Group A (FEV1≤50%)				
Total cost (SEM)	€ 4,635 (307)	€ 4,419 (320)	€ -216 (257)	0.63
QALY (SEM)	1.20 (0.014)	0.27 (0.011)	0.07 (0,010)	<0.001
Group B (FEV1>50%)				
Total cost (SEM)	€ 2,791 (165)	€ 1,830 (113)	€ -961 (195)	<0.0001
QALY (SEM)	1.54 (0.015)	1.56 (0.024)	0.02 (0.022)	0.53

Table V. *Cost-effectiveness results: first 24 months od current therapy (CT) vs last 24 months of tiotropium monotherapy (MT)*
SEM = Standard Error Mean

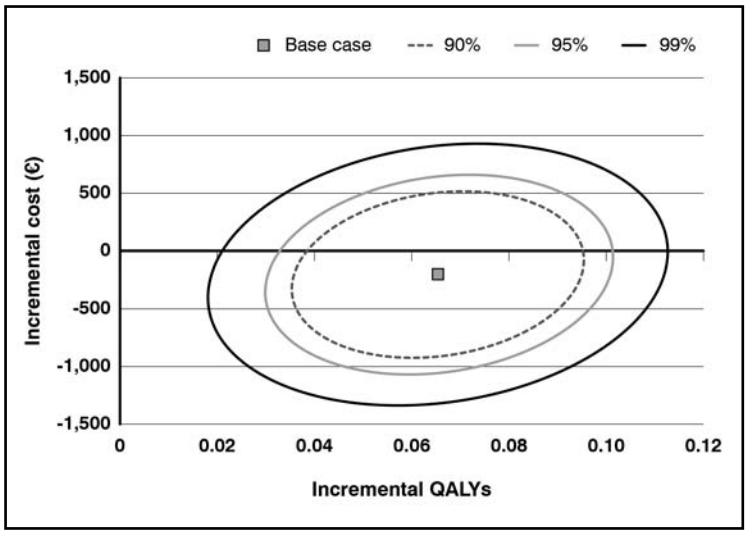

Figure 2. *Confidence ellipses for different significant levels (MT vs. CT) in FEV1≤50% patients (A)*

Among patients completing treatment course, MT strategy was observed to be dominant in almost 30% (A) and 36% (B) of subjects while only in 2% (A) and 7% (B) of cases an increase in costs was associated with a worsening of quality of life. Statistical analyses show that for severe COPD patients (A) MT strategy was more effective for any confidence level (Figure 2) and cost-effective for willingness-to-pay values of at least 10,000 € (Figure 3).

For mild-to-moderate COPD patients (B) MT strategy was less expensive for any confidence level (Figure 4): CEAC did not asymptote to 1 since there is a 20% of probability that MT strategy does not involve health gains (Figure 5).

DISCUSSION

Data from the present investigation lead to several considerations. Firstly, COPD patients referring for the first time to a Specialist Centre usually show a disease condition which is already characterized by a relevant clinical and a pharmacoeconomic impact; secondly, this impact is not merely dependent of their limitation in lung function. Actually, subjects suffering from mild-to-moderate COPD showed an unexpectedly remarkable impact. Moreover, the home therapy followed over the last 12 months before the first visit to the Centre (such as in the period year -1 vs. year 0 values) did not produce any substantial improvement of clinical and pharmacoeconomic variables, independently of the severity of their lung function impairment.

The switch to tiotropium 18 µg od monotherapy on a regular basis consented a progressively and substantial improvement of economic variables, and this strategy proved highly effective and the most convenient particularly in most severe patients (Group A)

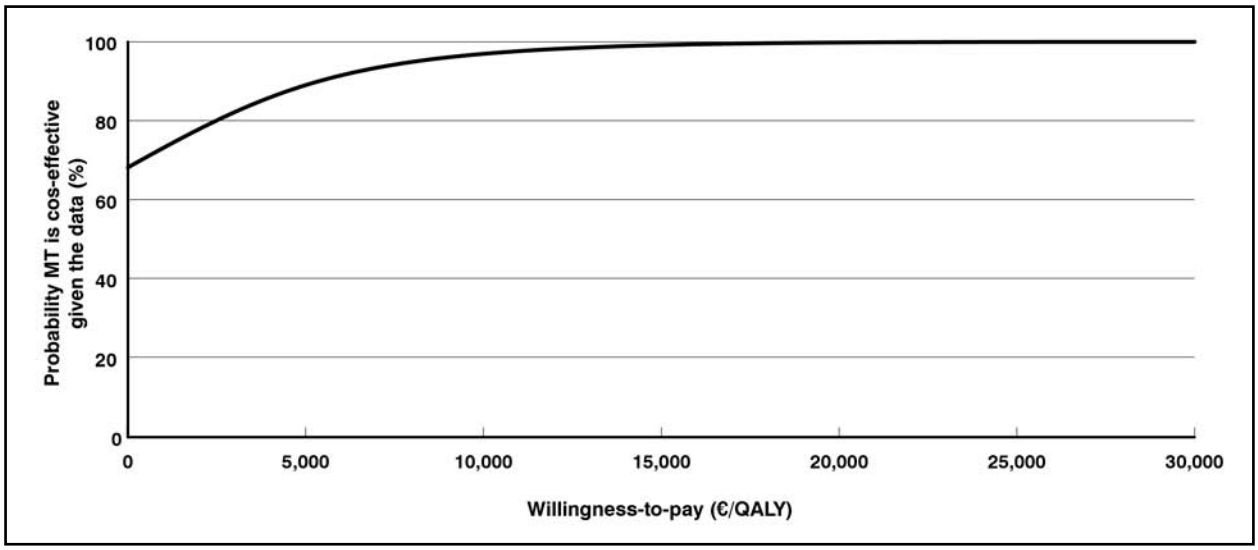

Figure 3. *Cost-effectiveness acceptability curve (MT vs. CT) for FEV1≤50% patients (A)*

The present study was designed in order to also investigate in real life the opportunity and the convenience of an earlier therapeutic intervention in COPD. Data obtained tend to support and emphasize both the utility and the convenience of the earlier regular and long-term treatment of COPD, i.e. starting when the functional (and presumably also the structural damage) is lower. Furthermore, the positive trend of pulmonary function coupled with the global improvement of pharmaco-economic outcomes is a feature of further great value from this point of view.

The introduction of tiotropium as a daily therapeutic strategy enables a significant minimization of the socio-economic impact of COPD, which proves substantial and systematic when COPD is severe.

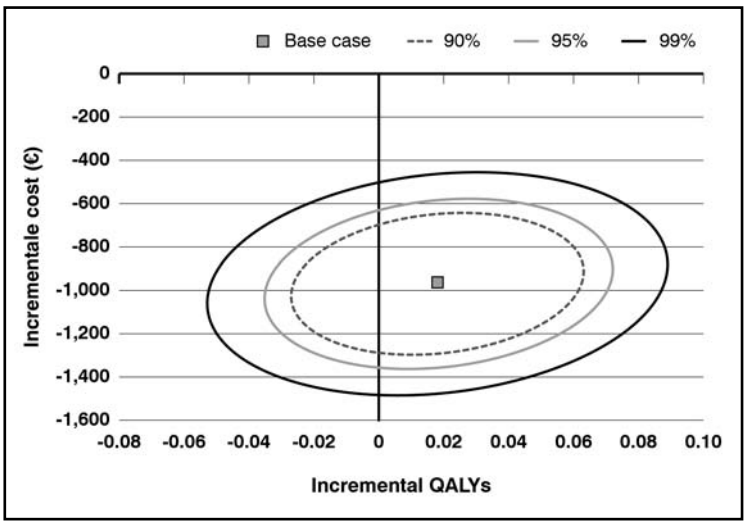

Figure 4. *Confidence ellipses for different significant levels (MT vs. CT) in FEV1>50% patients (B)*

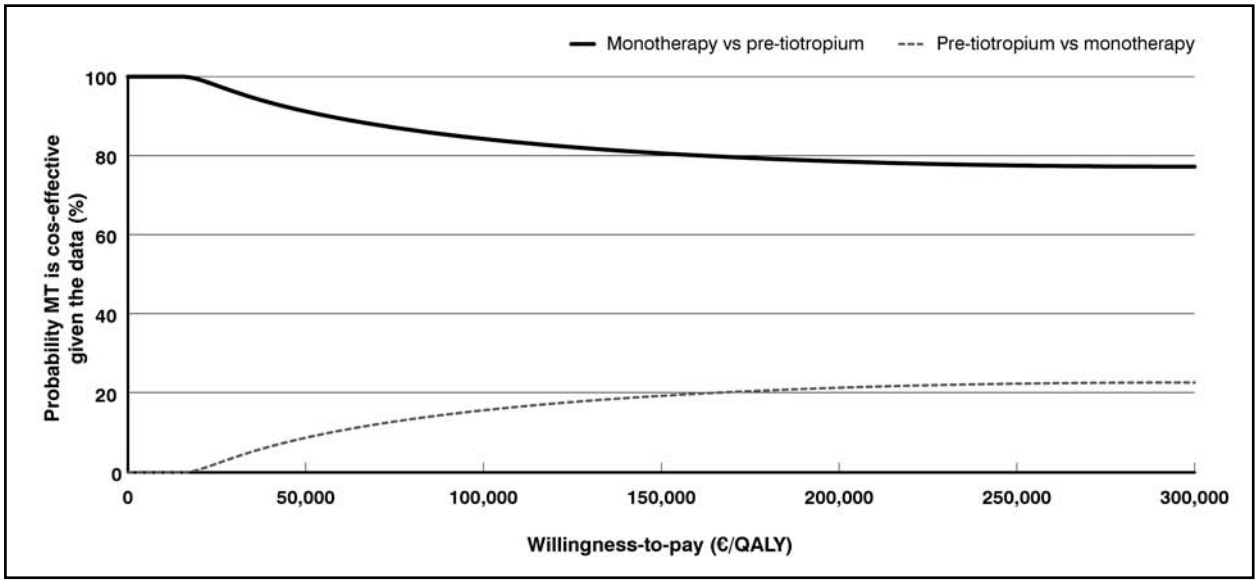

Figure 5. *Cost-effectiveness acceptability curve (MT vs. CT) for FEV1>50% patients (B)*

CONCLUSIONS

Results from the present study suggest that adoption of tiotropium as unique treatment in mild-to-moderate and severe COPD patients yields significant costs savings and has a beneficial effect on evaluated quality of life.

Monotherapy with tiotropium 18 μg daily reduced overall COPD management costs both in severe and in mild-to-moderate patients in our sample, and resulted cost-effective. Statistical analysis confirms the reliability of these results particularly in severe COPD, being the confidence on the cost-effectiveness in mild-to-moderate COPD about 80%. It is presumable that also in milder conditions this strategy would play a critical role in the natural history of COPD.

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