Netherlands
The Journal of Medicine

REVIEW

Which long-acting bronchodilator is most cost-effective for the treatment of COPD?

M. Hoogendoorn[1]*, B.S. Kappelhoff[2], J.A. Overbeek[3], E.F.M. Wouters[4], M.P.M.H. Rutten-van Mölken[1]

[1]Institute for Medical Technology Assessment (iMTA), Erasmus University, Rotterdam, the Netherlands, [2]Boehringer Ingelheim bv, Alkmaar, the Netherlands, [3]PHARMO institute, Utrecht, the Netherlands, [4]Department of Respiratory Medicine, Maastricht University Medical Centre, Maastricht, the Netherlands, *corresponding author: tel. +31(0)10 408 8871, fax: +31 (0)10 408 9081, e-mail: hoogendoorn@bmg.eur.nl

ABSTRACT

Background: The aim of this study was to estimate the cost-effectiveness of tiotropium versus salmeterol to inform decision making within the Dutch healthcare setting.

Methods: A previously published, validated COPD progression model was updated with new exacerbation data and adapted to the Dutch setting by including Dutch estimates of healthcare use for COPD maintenance treatment and Dutch unit costs. Exacerbation data from the POET-COPD trial were combined with evidence from earlier tiotropium studies using Bayesian meta-analysis. The model-based analysis was performed using a one- and five-year time horizon. Main health outcomes were the number of exacerbations and quality-adjusted life years (QALYs).

Results: One-year costs per patient from the healthcare perspective were €1370 for tiotropium and €1359 for salmeterol; a difference of €11 (95% uncertainty interval (UI): -198-212). The annual number of exacerbations was 0.068 (-0.005-0.140) lower in the tiotropium group. The number of QALYs in the tiotropium group was 0.011 (-0.019-0.049) higher, resulting in an incremental cost-effectiveness ratio (ICER) of €1015 per QALY. After five years, the difference in exacerbations, QALYs and costs between the tiotropium and salmeterol group were -0.435 (-0.915-0.107), 0.079 (-0.272-0.520) and €-277 (-1586-1074), respectively, indicating that tiotropium was more effective and less costly. Using a societal perspective, tiotropium dominated salmeterol both after one and five years.

Conclusion: Tiotropium reduced exacerbations and exacerbation-related costs. After one year the cost per QALY of tiotropium compared with salmeterol was very low, while after five years tiotropium was found to dominate salmeterol.

KEYWORDS

Costs, exacerbations, model, quality-adjusted life years, salmeterol, tiotropium

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common and treatable disease characterised by persistent airflow limitation that is usually progressive and is accompanied by extrapulmonary effects that can lead to important comorbidities. In the Netherlands the prevalence of COPD is estimated to be as high as 4.1-5.4% for the population above 40 years[1-3] making COPD one of the leading causes of disability and mortality.[4,5] The burden of COPD is substantial and expected to increase in the near future due to ageing of the population and an increase in the prevalence of smoking among women in the past decades. Given the limited healthcare budgets, the need for information on efficient treatment options for COPD in terms of both effects and costs is high. Data on costs and cost-effectiveness are very relevant for guideline development and policy making, because they allow calculating the total costs of using one treatment instead of another treatment and the total effect in return for incurring these costs.

An important part of the treatment of COPD consists of pharmacotherapy to relieve symptoms, improve quality of life and prevent exacerbations. Current national and international guidelines for the treatment of COPD recommend the use of long-acting bronchodilating agents for patients with moderate to very severe COPD (according to the GOLD guidelines).[6-8] Available long-acting bronchodilating agents can be divided into long-acting

beta-agonists (salmeterol, formoterol and indacaterol) and long-acting anticholinergic drugs (tiotropium).[9] Although the Dutch General Practitioners (NHG) guideline for COPD[7] expresses a slight preference for tiotropium in patients with more severe COPD or cardiac comorbidity, other guidelines do not favour one type of long-acting bronchodilator over the other,[6,8] because direct comparisons of both types of long-acting agents were limited or had a short duration.[10,11] Recently, however, results of a large multinational head-to-head comparison, the Prevention Of Exacerbations with Tiotropium (POET-COPD) trial, were published. This one-year trial in patients with moderate to very severe COPD and a history of at least one exacerbation in the previous year showed that tiotropium was more effective in preventing exacerbations than salmeterol.[12,13] The trial-based economic evaluation showed that tiotropium significantly reduced exacerbation-related costs, but total costs were higher than in the salmeterol group.[14] The costs per exacerbation avoided were estimated to be €1961, using the perspective of the German Statutory Health Insurance (SHI). The aim of the current study was to estimate the cost-effectiveness of tiotropium versus salmeterol in the Dutch setting. Due to the very small number of Dutch COPD patients included in the trial (n=2) a subgroup analysis on Dutch patients in the POET-COPD trial was not possible. Instead of such a trial-based analysis, a model-based analysis was done using a previously published COPD cost-effectiveness model.[15-17] The exacerbation probabilities and healthcare use in this model were updated with data from the POET-COPD trial.[13] This updated model was used to estimate the cost-effectiveness of tiotropium versus salmeterol in the Netherlands, to extrapolate results up to five years and to calculate quality-adjusted life-years (QALYs).

METHODS

Model structure

The Markov model used has been described in detail previously.[15-17] The model is a state-transition model that simulates how a cohort of COPD patients progresses over time. It has four states, three COPD severity states, moderate, severe and very severe COPD defined by the lung function boundaries of the GOLD guidelines,[6] and death. The starting distribution of patients over the three COPD severity states was based on Dutch data: 75% in moderate, 21% in severe and 4% in very severe COPD.[18] In each COPD severity state patients have a risk to experience a non-severe or severe exacerbation. The model has a cycle length of one month, which means that each month patients have a certain probability to move between states and experience an exacerbation. Healthcare costs, mortality rates and quality of life (utilities) were assigned to the COPD states and the exacerbations. The time horizon of the model can vary between one and five year. The model was validated in previous publications.[14,15]

The model is filled with data on the probability to have an exacerbation and the probability that an exacerbation is severe. In the POET-COPD trial an exacerbation was defined as an increase or new onset of more than one symptom (cough, sputum, wheezing, dyspnoea, chest tightness), with at least one symptom lasting at least three days requiring treatment with systemic steroids or antibiotics (non-severe or moderate exacerbation) or hospitalisation (severe exacerbation). Exacerbation data from the tiotropium group of the POET-COPD trial were synthesised with evidence on COPD exacerbations from previous tiotropium studies[10,19,20] by performing a Bayesian fixed-effects meta-analysis. The relative risks of salmeterol versus tiotropium obtained from the salmeterol-controlled tiotropium trials[10,13] were applied to the pooled exacerbation probabilities of tiotropium to obtain the probabilities for salmeterol. The exacerbation probabilities are shown in *table 1*. The risk of experiencing an exacerbation varies by COPD state and treatment group and was assumed to be constant over time.

The model is also filled with probabilities to move between states. These transition probabilities were not affected by the POET-COPD trial and remained the same as previously published.[17] The probabilities to move to another COPD severity stage for the first year were obtained from the pooled patient-level data of six tiotropium trials.[10,19,20] The transition probabilities for salmeterol were calculated in the same way as the exacerbation probabilities by applying the relative risks observed in the two trials directly comparing tiotropium and salmeterol with the transition probabilities of tiotropium.[9,12] The resulting probabilities to move to a more severe COPD state in the first year were slightly higher for salmeterol compared with tiotropium. The decline in lung function after the first year was assumed to be 52 ml per year in both treatment groups.[16]

Table 1. *Mean (SE) monthly exacerbation probabilities by treatment group after update with data from the POET-COPD trial using Bayesian fixed-effects meta-analysis**

	Probability to experience an exacerbation		Probability that the exacerbation is severe, given an exacerbation	
	Tiotropium	Salmeterol	Tiotropium	Salmeterol
Moderate COPD	.0483 (.002)	.0495 (.004)	.1098 (.014)	.1093 (.026)
Severe COPD	.0624 (.001)	.0681 (.002)	.1697 (.010)	.1776 (.015)
Very severe COPD	.0765 (.003)	.0844 (.004)	.2439 (.017)	.2738 (.028)

***Reproduced with permission of the European Respiratory Society.[14]**

The probabilities to die within each COPD severity state were derived from the Dutch all-cause age- and sex-specific mortality rates among COPD patients.[21,22]

Input data with regard to quality of life consisted of the utility values per COPD severity in the stable state[23] and the proportional reduction in the utility during an exacerbation. During the month in which patients experienced an exacerbation the utility value in the stable state was reduced by 15% for a non-severe exacerbation and by 50% for a severe exacerbation.

Perspective

The cost-effectiveness study for the Dutch setting was performed from two different perspectives: 1) the Dutch healthcare perspective, including all national healthcare insurance costs and 2) the societal perspective, including all national healthcare insurance costs, patient co-payments, travel expenses and costs of absence from paid work.

Resource use and costs

The model distinguishes two types of healthcare utilisation: healthcare use for maintenance treatment (*table 2*) and for a non-severe or severe exacerbation (*table 3*). Exacerbation-related resource use and medication use for maintenance treatment were obtained from all patients included in the trial-based cost-effectiveness study of the POET-COPD trial.[14] Other healthcare utilisation associated with maintenance treatment was based on Dutch data sources, which can be found in *table 2*. The number of GP visits for maintenance treatment of COPD was calculated as the total number of GP visits among COPD patients minus the average number of visits for age-matched controls without COPD as obtained from the PHARMO database[26] minus the exacerbation-related visits as observed in the POET-COPD trial. The number of visits to the respiratory specialist for maintenance treatment was based on the average number of visits to

Table 2. *Annual costs of maintenance treatment in the Netherlands, in 2011* €

Costs of maintenance therapy (per year)	Unit cost	Moderate COPD				Severe COPD				Very severe COPD			
		Resource use		Total cost		Resource use		Total costs		Resource use		Total costs	
		Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Outpatient visits to general practitioner[26]	29.27	5.09	0.09	149.01	2.68	4.43	0.14	129.56	4.0	4.09	0.32	119.84	9.33
Home visits by general practitioners[26]	44.95	0.57	0.03	25.43	1.37	1.11	0.09	49.74	3.84	2.34	0.25	105.17	11.14
Outpatient visits to respiratory specialists[27,28]	75.27	0.26	0.05	19.26	4.14	2.37	0.21	178.66	15.90	2.37	0.21	178.66	15.90
Spirometries[24]	17.67	0.33	0.07	5.83	1.17	1.0	0.20	17.67	3.53	1.0	0.20	17.67	3.53
Influenza vaccination (%)[25]	15.71	0.73	0	11.48	0.05	0.73	0	11.48	0.05	0.73	0	11.48	0.05
Days antibiotics used*	0.53	2.75	0.34	1.46	0.18	2.67	0.39	1.42	0.21	1.34	0.26	0.71	0.14
Days systemic steroids used*	0.06	7.36	0.85	0.44	0.05	10.56	1.05	0.64	0.06	11.08	2.44	0.67	0.15
Days short-acting beta-agonists used*	0.17	6.73	0.82	1.18	0.14	8.87	0.98	1.55	0.17	9.95	2.30	1.74	0.40
Days short-acting anticholinergics used*	0.30	1.39	0.34	0.41	0.10	1.44	0.38	0.43	0.11	2.91	1.21	0.87	0.36
Days inhaled corticosteroids used*	0.68	141.23	2.99	95.47	2.02	156.38	3.24	105.72	2.19	139.72	7.15	94.45	4.83
Days theophylline used*	0.04	60.60	2.24	2.50	0.09	76.67	2.65	3.16	0.11	73.07	2.64	3.01	0.11
Days mucolytics used*,#	0.71	9.03	0.91	6.41	0.65	12.00	1.16	8.51	0.82	11.06	2.29	7.85	1.62
Days oxygen used*	4.34	0.86	0.26	3.73	1.13	3.71	0.63	16.09	2.73	5.81	1.72	25.20	7.46
Travel costs (km)*,#	0.21	7.39	1.48	1.55	0.31	21.48	4.30	4.49	0.90	21.12	4.22	4.42	0.88
Total costs healthcare perspective				316.21	5.74			516.11	17.56			559.47	23.57
Total costs societal perspective				324.16	5.79			529.12	17.60			571.73	23.64

*Source resource use: all patients in POET-COPD trial; #Costs only included using the societal perspective.

Table 3. *Costs per COPD exacerbation in the Netherlands, in 2011* €

Per exacerbation	Unit cost	Non-severe exacerbation				Severe exacerbation			
		Resource use		Costs		Resource use		Costs	
		Mean	SE	Mean	SE	Mean	SE	Mean	SE
ICU days	2282.23	na	na	na	na	0.76	0.18	1734.49	408.52
Non-ICU days	228.14	na	na	na	na	12.39	0.33	2825.92	75.90
Ambulance rides	346.05	na	na	na	na	0.31	0.02	107.27	5.88
Outpatient visits to general practitioners	29.27	0.58	0.01	17.10	0.42	0.40	0.03	11.72	0.81
Outpatient visits to respiratory specialists	75.27	0.60	0.02	44.86	1.23	0.46	0.03	34.93	2.13
Outpatient visits to non-respiratory specialists	75.27	0.04	0.01	3.12	0.39	0.07	0.01	4.99	0.80
Outpatient visits to other healthcare providers	37.64	0.03	0.01	1.13	0.26	0.03	0.01	1.13	0.30
ER visits not followed by hospital admission	157.86	0.04	0.03	6.31	0.47	0.20	0.02	31.57	2.53
Ambulance rides to ER	346.05	0.01	0.02	3.46	0.69	0.12	0.01	41.53	4.50
Days antibiotics	0.53	8.54	0.34	4.54	0.18	13.19	1.02	7.0	0.54
Days systemic steroids	0.06	6.82	0.38	0.41	0.02	14.89	1.25	0.90	0.08
Days short-acting beta-agonists	0.17	0.31	0.13	0.05	0.02	1.44	0.47	0.25	0.08
Days short-acting anticholinergics	0.30	0.39	0.13	0.12	0.04	2.73	0.34	0.82	0.10
Days inhaled corticosteroids	0.68	3.45	0.45	2.33	0.30	8.40	1.29	5.68	0.87
Days theophylline	0.04	2.02	0.36	0.08	0.01	11.13	1.43	0.46	0.06
Days mucolytics#	0.71	2.26	0.22	1.61	0.15	6.95	0.77	4.93	0.55
Travel costs (km)#	0.21	5.45	1.09	1.14	0.23	5.62	1.12	1.17	0.23
Costs for days absence paid work#	304.27	1.01	0.06	307.26	17.79	2.65	0.26	806.60	80.32
Total costs of exacerbation healthcare perspective				83.52	1.65			4808.67	415.59
Total costs of exacerbation societal perspective				393.52	17.87			5621.38	426.28

na=not applicable; #costs only included using the societal perspective.

specialists specified by level of dyspnoea,[27] the percentage of patients visiting the respiratory specialist[28] and the exacerbation-related visits to the respiratory specialist in the POET-COPD trial. Unit costs for contacts with the different healthcare providers were obtained from the Dutch costing manual[29] and updated to the year 2011.[30] The unit costs for an inpatient hospital day for COPD were obtained from a Dutch clinical trial.[31] All medication costs were based on the list prices of 2011 minus the clawback including 6% VAT as obtained from the Taxe (October 2011). The average costs of study medication were calculated as the weighted average costs per daily defined dose (DDD) of all available devices of either tiotropium or salmeterol using the total DDDs in the Netherlands as a weight. This resulted in an average cost per day of €1.35 for tiotropium and €0.91 for salmeterol. All medications were fully reimbursed, except for the mucolytics. Therefore medication costs from the healthcare and societal perspective were equal except for the mucolytics for which the costs were only included in the societal perspective.

Health outcomes

The main health outcomes of the model were the total number of non-severe and severe exacerbations and the total number of QALYs. The total number of QALYs was calculated as the sum of the annual number of life years (=number of patients alive) weighted by the quality of life during these years using the utility weights specified by COPD severity state. For each exacerbation a reduction in utility weights was applied.

Cost-effectiveness

The incremental cost-effectiveness ratios (ICERs) were calculated as the difference in total costs between the tiotropium and the salmeterol group divided by the difference in the number of QALYs or the difference in exacerbations resulting in the costs per QALY gained and the costs per exacerbation avoided, respectively.

Base-case analysis

The base-case analysis was performed for a one-year and five-year time horizon, both for the healthcare and the

societal perspective. In the five-year analysis costs were discounted with 4%, effects with 1.5%.[32]

Sensitivity analyses

Several one-way sensitivity analyses were performed on changes in the starting distribution of the patients over the COPD severity states (100% in either moderate, severe or very severe COPD), different methods of meta-analysis for the exacerbation probabilities (frequentist fixed- and random-effects meta-analysis) and different discount rates (0% or 4% discounting for both costs and effects). Furthermore, the impact of three other assumptions was tested: assuming no difference in exacerbation risk between tiotropium and salmeterol after one year, using different unit costs for an inpatient hospital day based on the Dutch costing manual (€478) and applying a 50% smaller reduction in utility due to an exacerbation. All one-way sensitivity analyses were performed from the healthcare perspective. The model had a fully probabilistic design, which means that uncertainty around the transition and exacerbation probabilities, utilities and costs was taken into account.[15] After making 5000 random draws from the probability distributions of the uncertain parameters, the model was run for each set of parameters. This resulted in 5000 different outcomes for effects and costs, which were plotted on cost-effectiveness planes (CE plane). A CE plane is an x-y diagram with the x-axis representing the difference in health outcome between tiotropium and salmeterol and the y-axis representing the difference in costs. The information in the CE plane was summarised in cost-effectiveness acceptability curves, which show the probability that the incremental cost-effectiveness ratio of tiotropium falls below a range of ceiling ratios. These ceiling ratios reflect the maximum the decision makers would be willing to invest to gain one QALY.

Table 4. *One-year and five-year results from the model-based cost-effectiveness analysis, healthcare perspective (costs in 2011 €)*

	Tiotropium*	Salmeterol*	Difference*
One year:			
Total exacerbations	0.647 (0.614-0.681)	0.716 (0.648-0.780)	-0.068 (-0.410-0.005)
Quality-adjusted life-years	0.747 (0.726-0.763)	0.736 (0.700-0.756)	0.011 (-0.019-0.049)
Costs of study medication	485 (473-491)	328 (313-332)	157 (144-173)
Costs of maintenance therapy	390 (371-410)	410 (378-443)	-19 (-57-18)
Exacerbation-related costs	495 (401-600)	621 (471-749)	-127 (-320-56)
Total costs	1370 (1268-1482)	1359 (1191-1544)	11 (-198-212)
Five year:			
Total exacerbations	3.189 (2.937-3.400)	3.624 (3.133-4.035)	-0.435 (-0.915-0.107)
Quality-adjusted life-years	3.355 (3.108-3.522)	3.276 (2.869-3.517)	0.079 (-0.272-0.520)
Costs of study medication	2130 (1987-2222)	1440 (1273-1525)	690 (514-885)
Costs of maintenance therapy	1889 (1726-2046)	1996 (1733-2226)	-107 (-386-212)
Exacerbation-related costs	2600 (2103-3148)	3459 (2581-4458)	-860 (-1970-178)
Total costs	6618 (5957-7296)	6895 (5757-8073)	-277 (-1586-1074)

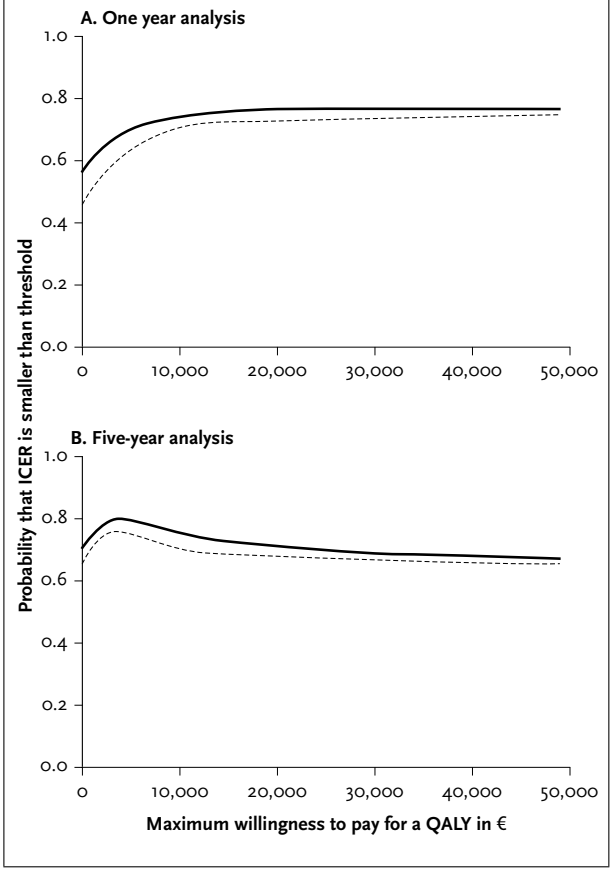
***Data are mean (95% uncertainty interval)**

RESULTS

One-year results

After one year, treatment with tiotropium resulted in 0.011 (95% uncertainty interval (UI) -0.019-0.049) more QALYs and 0.068 (95% UI -0.005-0.14) less exacerbations compared with salmeterol (*table 4*). The reduction in severe exacerbations was 0.025 (95% UI -0.003-0.055). As a result the total exacerbation-related costs were more than 20% lower in the tiotropium group compared with the salmeterol group. Hospitalisation-related exacerbation costs were reduced by 22%, while other exacerbation-related costs decreased by 12%. Costs for study medication were €157 (95% UI 144-173) higher for tiotropium. The total costs per patient from the healthcare perspective were €1370 (95% UI 1268-1482) in the tiotropium group and €1359 (95% UI 1191-1544) in the salmeterol group, resulting in a difference of €11 (95% UI -198-212). The incremental cost-effectiveness ratios were €162 for the cost per exacerbation avoided and €1015 for the costs per QALY. From a societal perspective the total costs per patient were €1628 (95% UI 1520-1747) for the tiotropium group and €1650 (95% UI 1463-1856) for the salmeterol group, a difference of €-22 (95% UI -251-197). In the tiotropium group costs for productivity loss due to an exacerbation were €33 (95% UI -16-83) lower compared with salmeterol. Because tiotropium dominated salmeterol from a societal perspective, i.e. was more effective and less costly, no ratios have been calculated. The CE plane from the healthcare perspective using QALYs as outcome showed that in 41% of the simulations treatment with tiotropium resulted in more effects and higher costs, while in 36% tiotropium was more effective and cost saving compared with salmeterol. Using exacerbations as outcome these percentages were 51% and 45%, respectively. *Figure 1* shows the acceptability curve for the costs per QALY from the two perspectives. For a maximum-willingness-to-pay for a QALY of €20,000, the probability that tiotropium would be cost-effective was 73% from a healthcare perspective and 76% from a societal perspective.

Figure 1. *Acceptability curve for the costs per QALY gained for A) one-year analysis and B) five-year analysis (dashed line: healthcare perspective, black line: societal perspective)*



Five-year results

The model results using a time horizon of five years showed that the gain in QALYs due to tiotropium was 0.079 (95% UI -0.272-0.520) compared with salmeterol (*table 4*). The total number of exacerbations was almost 14% lower in the tiotropium group than in the salmeterol group. The reduction in severe exacerbations was significant, 0.184 (95% UI 0.008-0.367). From a healthcare perspective the total five-year costs were €6618 (95% UI 5957-7296) for tiotropium and €6895 (95 UI 5757-8073) for salmeterol, a difference of €-277 (95% UI -1586-1074) (*table 4*). The higher costs of tiotropium were completely offset by the savings in exacerbation-related costs. From a societal perspective the difference in costs between tiotropium and salmeterol was €-409 (95% UI -2040-1180). Tiotropium reduced costs for productivity loss for exacerbations by €120 (95% UI-182-433) (12% reduction) compared with salmeterol. Both from a healthcare and societal perspective, tiotropium dominated salmeterol, so no cost-effectiveness ratios were calculated. The acceptability curve for the five-year analysis (*figure 1*) showed that the probability that tiotropium was cost-effective at a threshold value of €20,000 per QALY was 67% from a healthcare perspective and 70% from a societal perspective.

One-way sensitivity analyses

One-year results were most sensitive to the severity distribution assumed at baseline. The incremental cost-effectiveness ratios for both the costs per QALY and the costs per exacerbation avoided increased when all patients had moderate COPD at start of treatment, whereas tiotropium was dominant over salmeterol when all patients had severe or very severe COPD at the start. Using the exacerbation probabilities based on random-effects meta-analysis and using the higher unit costs of an inpatient hospital day also resulted in tiotropium being more effective and less costly than salmeterol. For all remaining one-year sensitivity analyses the ICERs were well below €20,000 per QALY. For the five-year analyses tiotropium was more effective and less costly in all sensitivity analyses, except one. If no exacerbation benefit for tiotropium was assumed after the first year, the costs per QALY would become €130.

DISCUSSION

The current study aimed to estimate the cost-effectiveness of tiotropium versus salmeterol in the Dutch setting. From a healthcare perspective the one-year total costs for tiotropium were €11 (95% UI -198-212) higher. The higher medication costs (€157 per patient) for tiotropium were for more than 80% compensated by a reduction in costs for COPD exacerbations. The ICERs were €162 for the costs per exacerbation avoided and €1015 for the costs per QALY. If the reduction in costs due to productivity loss during exacerbations in the tiotropium group were also included, as was done in the analysis from the societal perspective, the higher medication costs for tiotropium would be completely compensated, resulting in tiotropium being more effective and less costly than salmeterol.

Using a five-year time horizon, the total costs per patient from a healthcare perspective were €277 (95% UI -1074;1586) lower for tiotropium compared with salmeterol. The higher medication costs of tiotropium (€690 per patient in five years) were fully offset by the reduction in costs of COPD exacerbations. From a societal perspective the total five-year costs in the tiotropium group were €409 (95% UI -2040-1180) lower compared with the salmeterol group. As a result tiotropium dominated salmeterol irrespective of the perspective used. Five-year results were better than one-year results because in the five-year analyses the impact of disease progression of COPD was also taken into account. Because the reduction in exacerbations in tiotropium compared with salmeterol

was greater in patients with severe and very severe COPD, the difference in effect between tiotropium and salmeterol became greater when patients progressed towards more severe stages of COPD.

In all one-year sensitivity analyses, the ICER remained below €20,000. The results were most sensitive to the severity of COPD at the start of treatment, i.e. tiotropium was dominant in patients with severe and very severe COPD, whereas in moderate COPD the costs per exacerbation avoided were €527 and the costs per QALY €3200. Results were also sensitive to the unit costs for an inpatient hospital day. Using the reference unit costs of a non-ICU hospital day from the Dutch costing manual[29] (€478 per day in 2011) resulted in tiotropium dominating salmeterol. Because we had indications that the unit costs for a non-ICU inpatient hospital day for COPD were lower than this reference price, we used a lower unit cost of €228 in the base-case analysis. This lower estimate of the costs of an inpatient hospital day was based on a clinical trial investigating the effectiveness of early assisted discharge in patients hospitalised for a COPD exacerbation.[31] Because the patients in that trial had exacerbations that were probably less severe than the average exacerbation that requires a hospital admission, our estimate of the unit costs used in the base-case analysis is likely to be a minimum estimate of the costs of an inpatient hospital day for COPD. Therefore, the results of the base-case analyses are conservative. The five-year sensitivity analyses showed that tiotropium was dominant in all cases, except one. Results were most sensitive to the assumption that was made about the difference in exacerbation probabilities between the two treatments after the first year. In the base-case this difference was assumed to remain constant during year 2 to 5. If, in the extreme case, we did not assume any additional exacerbation benefit of tiotropium compared with salmeterol after the first year, tiotropium would no longer be dominant. The costs per QALY would become €130, still a very low ratio.

The updated model used in the current study was validated by using the exacerbation probabilities, COPD severity distribution and time horizon of the POET-COPD trial as input for the model.[14] Comparison of the model results with the outcomes of the trial showed that the model was able to reproduce the difference in total number of exacerbations and severe exacerbations in the trial. The resulting cost per QALY gained was also comparable.[14] The model could not be validated for the five-year time horizon. The decline in lung function of 52 ml per year that was assumed after the first year may be relatively high given recent publications.[33-35] The impact of this assumption on the results is, however, limited because the same annual decline was used for both treatment options.

A recent review on pharmacological maintenance treatment of COPD found six studies investigating the cost-effectiveness of tiotropium versus salmeterol, one for the Dutch setting.[36] All of these studies were modelling studies, mostly based on the same model as used in this study. Tiotropium was found to be more effective and less costly in four out of the six studies, including the study for the Netherlands. The other two studies reported cost-effectiveness ratios below €4118 per QALY gained. The difficulty with these modelling studies was that input data for the difference in exacerbations were obtained from studies directly comparing tiotropium and salmeterol that had a short duration and were underpowered to detect a difference in COPD exacerbations.[10] The current study showed that update of the input data of the model with exacerbation data from the large POET-COPD trial did not change the conclusions. Tiotropium was still very cost-effective compared with salmeterol and even cost saving using a societal perspective or a five-year time horizon.

The severity distribution for COPD used in the current version of the model was based on the degree of airflow limitation. Recently the GOLD committee proposed a new grading of COPD severity based on airflow obstruction, symptoms and exacerbations.[37] Although the new classification reflects the complexity of COPD better than the classification based on airflow limitation alone, evidence on the prognostic value of the new classification in predicting future health outcomes is lacking. If in the future treatment effects and cost-effectiveness results are found to be different between the severity classes of this new classification, changes in the structure of the model need to be considered.

Up to the publication of the POET-COPD trial most international and national guidelines did not specify a preference for either long-acting anticholinergics or long-acting beta-agonist as evidence on difference in exacerbations was still limited. Only the NHG practice guideline 'COPD' reported a preference for tiotropium in a specific subgroup of patients.[7] The new available information on the difference in effects between tiotropium and salmeterol from the POET-COPD trial and the difference in costs from the current study can contribute to future guideline development and policy making for COPD in the Netherlands.

In conclusion, both over a one- and five-year time horizon tiotropium was found to reduce exacerbations compared with salmeterol among patients with moderate to very severe COPD, leading to a reduction in exacerbation costs. After one-year the total costs for tiotropium were slightly higher than for salmeterol leading to a cost per QALY of

€1015, which is regarded to be very cost-effective in the Netherlands. After five years the higher drug costs for tiotropium were completely compensated by the savings in exacerbation-related costs, resulting in tiotropium being more effective and cost saving.

FUNDING

This study was financially supported by Boehringer Ingelheim

REFERENCES

1. Bischoff EW, Schermer TR, Bor H, Brown P, van Weel C, van den Bosch WJ. Trends in COPD prevalence and exacerbation rates in Dutch primary care. Br J Gen Pract. 2009;59:927-33.
2. Gommer AM, Poos MJJC, eds. Cijfers COPD (Prevalentie, Incidentie En Sterfte) Uit VTV 2010. in Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid. RIVM, Bilthoven, 2010.
3. van der Lucht F, Polder JJ, eds. Van Gezond Naar Beter. Kernrapport Van De Volksgezondheid Toekomst Verkenning VTV-2010. National Institute of Public Health and the Environment (RIVM), Bilthoven, version 1.0, 25 March 2010.
4. Poos MJJC, ed. Waaraan Overlijden Mensen in Nederland? in: Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid. RIVM, Bilthoven, 2008.
5. Gommer AM, Hoeymans N, Poos MJJC, eds. Wat is De Ziektelast in Nederland? in: Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid. RIVM, Bilthoven, 2010.
6. Global Initiative for Chronic Obstructive Lung Disease. Workshop Report: Global Strategy for the Diagnosis, Management and Prevention of COPD: Updated 2009; http://www.goldcopd.com (Accessed September 2009).
7. NHG-Standaard COPD. Nederlands Huisartsen Genootschap, Utrecht, 2007.
8. Richtlijn Diagnostiek En Behandeling Van COPD. Kwaliteitsinstituut voor de Gezondheidszorg CBO, Utrecht, 2010.
9. Diamant Z, Tarasevych S, Clarke GW. New and existing pharmacotherapeutic options for persistent asthma and COPD. Neth J Med. 2011;69:486-99.
10. Brusasco V, Hodder R, Miravitlles M, Korducki L, Towse L, Kesten S. Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. Thorax. 2003;58:399-404.
11. Briggs DD Jr, Covelli H, Lapidus R, Bhattycharya S, Kesten S, Cassino C. Improved daytime spirometric efficacy of tiotropium compared with salmeterol in patients with COPD. Pulm Pharmacol Ther. 2005;18:397-404.
12. Beeh KM, Hederer B, Glaab T, et al. Study design considerations in a large COPD trial comparing effects of tiotropium with salmeterol on exacerbations. Int J Chron Obstruct Pulmon Dis. 2009;4:119-25.
13. Vogelmeier C, Hederer B, Glaab T, et al. Tiotropium versus Salmeterol for the Prevention of Exacerbations of COPD. N Engl J Med. 2011;364:1093-103.
14. Hoogendoorn M, Al MJ, Beeh KM, et al. Cost-effectiveness of tiotropium versus salmeterol: the POET-COPD trial. Eur Respir J.; Published ahead of print June 14 2012, doi:10.1183/09031936.00027212.
15. Oostenbrink JB, Rutten-van Molken MP, Monz BU, FitzGerald JM. Probabilistic Markov model to assess the cost-effectiveness of bronchodilator therapy in COPD patients in different countries. Value Health. 2005;8:32-46.
16. Rutten-van Molken MP, Oostenbrink JB, Miravitlles M, Monz BU. Modelling the 5-year cost effectiveness of tiotropium, salmeterol and ipratropium for the treatment of chronic obstructive pulmonary disease in Spain. Eur J Health Econ. 2007;8:123-35.
17. Oostenbrink JB, Al MJ, Oppe M, Rutten-van Molken MP. Expected value of perfect information: an empirical example of reducing decision uncertainty by conducting additional research. Value Health. 2008;11:1070-80.
18. Hoogendoorn M, Feenstra TL, Schermer TR, Hesselink AE, Rutten-van Molken MP. Severity distribution of chronic obstructive pulmonary disease (COPD) in Dutch general practice. Respir Med. 2006;100:83-6.
19. Casaburi R, Mahler DA, Jones PW, et al. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. Eur Respir J. 2002;19:217-24.
20. Vincken W, van Noord JA, Greefhorst AP, et al. Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium. Eur Respir J. 2002;19:209-16.
21. Feenstra TL, Van Genugten ML, Hoogenveen RT, Wouters EF, Rutten-van Molken MP. The impact of aging and smoking on the future burden of chronic obstructive pulmonary disease: a model analysis in the Netherlands. Am J Respir Crit Care Med. 2001;164:590-6.
22. Hoogendoorn M, Rutten-van Molken MP, Hoogenveen RT, et al. A dynamic population model of disease progression in COPD. Eur Respir J. 2005;26:223-33.
23. Rutten-van Molken MP, Oostenbrink JB, Tashkin DP, Burkhart D, Monz BU. Does quality of life of COPD patients as measured by the generic EuroQol five-dimension questionnaire differentiate between COPD severity stages? Chest. 2006;130:1117-28.
24. Richtlijn Ketenzorg COPD. Stichting Ketenkwaliteit COPD. Van Zuiden Communications BV, Alphen aan den Rijn, 2005.
25. Tacken M, Mulder J, Visscher S, et al., eds. Monitoring Vaccinatiegraad Nationaal Programma Grieppreventie 2009. LINH/Scientific Institute for Quality of Healthcare, Nijmegen, 2010.
26. PHARMO Institute. Healthcare Utilization for Patients with a COPD Diagnosis (Known by GP) by GOLD Stage. PHARMO Report, Utrecht, 2011.
27. van Houtum L, Spreeuwenberg P, Heijmans M, eds. Zorgsituatie Van Mensen Met COPD. Rapportage 2010. NIVEL, Utrecht, 2011.
28. Heijmans MJWM, Spreeuwenberg P, Rijken PM, eds. Monitor Zorg- En Leefsituatie Van Mensen Met Astma En Mensen Met COPD. Trends En Ontwikkelingen Over De Periode 2001-2008. NIVEL, Utrecht, 2009.
29. Hakkaart-van Roijen L, Tan S, Bouwmans C, eds. Handleiding Voor Kostenonderzoek. Methoden En Referentieprijzen Voor Economische Evaluaties in De Gezondheidszorg. Geactualiseerde Versie 2010. Erasmus Universiteit, iMTA, Rotterdam, 2010.
30. Consumentenprijzen; prijsindex 2006=100. 2011; http://statline/cbs.nl/ (Accessed Nov 2011).
31. Utens CM, Goossens LM, Smeenk FW, et al. Effectiveness and cost-effectiveness of early assisted discharge for chronic obstructive pulmonary disease exacerbations: the design of a randomised controlled trial. BMC Public Health. 2010;10:618.
32. Rodenburg-van Dieten HEM, ed. Guidelines for Pharmaco-Economic Research. Dutch Healthcare Insurance Board, Diemen, 2005.
33. Vestbo J, Edwards LD, Scanlon PD, et al., ECLIPSE Investigators. Changes in forced expiratory volume in 1 second over time in COPD. N Engl J Med. 2011;365:1184-92.
34. Tashkin DP, Celli B, Senn S, et al., UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med. 2008;359: 1543-54.
35. Celli BR, Thomas NE, Anderson JA, et al. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. Am J Respir Crit Care Med. 2008;178:332-38.
36. Rutten-van Mölken MPMH, Goossens LMA. The cost-effectiveness of pharmacological maintenance treatment of chronic obstructive pulmonary disease (COPD): a review of evidence and methodology issues. PharmacoEconomics. 2012;30:1-32.
37. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. 2011; http://www.goldcopd.com (Accessed, May 2012).