

Cost-Effectiveness of Dual Bronchodilator Indacaterol/Glycopyrronium for COPD Treatment in China

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Background: Indacaterol/glycopyrronium (IND/GLY) is a once-daily dual bronchodilator for long-term treatment of patients with chronic obstructive pulmonary disease (COPD). The efficacy and safety of IND/GLY have been proved before, but the cost-effectiveness is unknown in China.

Purpose: This study assessed cost-effectiveness of IND/GLY comparing with salmeterol/fluticasone (SAL/FLU) and tiotropium.

Methods: A patient-level simulation model was established from Chinese payer perspective. Patient parameters were randomly simulated through resampling from parameter distributions based on clinical trials and China-specific cost data to represent individual level health state and health state transitions in the model. We simulated patient-level health state, costs, life years (LYs) and quality-adjusted life years (QALYs) of whole life horizon to evaluate the cost-effectiveness of IND/GLY comparing with SAL/FLU and tiotropium respectively.

Results: Comparing with SAL/FLU, IND/GLY resulted in 0.384 LYs and 0.255 QALYs gained. The incremental cost-effectiveness ratio (ICER) is -35,822 CNY/LY and the incremental cost-utility ratio (ICUR) is -53,834 CNY/QALY for IND/GLY versus SAL/FLU. Comparing with tiotropium, IND/GLY resulted in 0.232 LYs and 0.146 QALYs gained. The ICER is 39,729 CNY/LY and the ICUR is 63,246 CNY/QALY for IND/GLY versus tiotropium.

Conclusion: This study found that dual bronchodilator IND/GLY is cost-effective for stable COPD treatment in China from Chinese payer's perspective.

Keywords: chronic obstructive pulmonary disease; COPD, dual bronchodilator, cost-effectiveness analysis, China

Introduction

Chronic obstructive pulmonary disease (COPD) is one of most common chronic diseases in China.¹⁻³ There are nearly 100 million COPD patients in China.¹ COPD ranked in the top three leading cause of death in China.^{2,4} Each COPD patient in China spends 499 to 1932 USD on total costs annually.² Besides medical costs increasing, COPD patients have worse health status and worse quality of life compared with the normal population.⁵ The huge disease burden of COPD calls for more attention to long-term management of COPD patients in China.

In China, current inhaled treatments for stable COPD include bronchodilators and inhaled corticosteroids (ICS).⁶ Monotherapies of bronchodilators, including long-acting beta2/adrenergic receptor agonists (LABAs) and long-acting cholinergic/muscarinic antagonists (LAMAs), are used for initial treatment in mild to moderate patients,⁶ while a combination of ICSs and LABA (ICS/LABA) is recommended for COPD patients with

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high exacerbation risk or high blood eosinophil count.⁶ These inhaler therapies significantly improve lung function, reduce exacerbations and improve quality of life for COPD patients. In addition, combination therapy of two types of long-term bronchodilators (LAMA and LABA) performed better recently in clinical trials,^{7–11} hence it becomes a new choice for stable COPD patients with more severe symptoms.¹² IND/GLY, a once-daily dual bronchodilator for treatment of patients with COPD, which contains a fixed dose of 110ug of LABA indacaterol and 50 ug the LAMA glycopyrronium. Compared with monotherapy bronchodilators and ICS/LABA therapy, IND/GLY significantly improves lung function, reduces exacerbation and improves health status in trials in China and worldwide.^{13–16} Previous studies have shown cost-effectiveness of IND/GLY compared with other therapies from the payer's perspective in USA and Europe.^{17,18} However, China's medical system and medical service prices are completely different from the Western world.¹⁹ The cost-effectiveness of IND/GLY should be reassessed in the setting of China's medical system.

In this study, we aimed to assess the cost-effectiveness of a LABA/LAMA combination therapy IND/GLY for COPD management compared with the current single LAMA therapy and ICS/LABA combination therapy from Chinese payer's perspective using real-world data in China.

Method

Patient-Level Simulation Model

A patient-level simulation is a type of model that simulated health state transition at patient-level rather than cohort-level. In this model, patients entering the model were generated randomly with specific parameters of demographic data and health outcomes to represent different health state. Patient-level outcomes were determined based on random selection from specific distributions of parameters for target population with the model running. When compared with the traditional cohort-level Markov model, patient-level simulation model is assumed to be more flexible and more intuitive, as this model can capture heterogeneity in the patient population and simulate more health states.²³

Model Structure

We developed a patient-level simulation model for COPD patients using Microsoft Excel[®] software to simulate health states, costs and outcomes at individual level over time as shown in [Figure 1](#). One thousand individual-level virtual “patients” were randomly generated in this model.

Parameters that represent individual level health state were randomly assigned from the distributions derived from clinical trials and China-specific cost data. In the simulation, generated patients experienced disease progression and clinical events in every 6-month cycle in this model. Total costs, life years (LYs) and quality-adjusted life years (QALYs) of each patient was cumulated during time horizon of whole life time to evaluate the cost-effectiveness of IND/GLY and comparators respectively.

Model Parameters

IND/GLY as a representative of LABA/LAMA combination inhalation therapy, were compared with two another two current inhaled drugs for COPD. ICS/LABA combination salmeterol/fluticasone (SAL/FLU) (50/500µg, twice daily) and LAMA tiotropium (18µg, once daily) are most common inhaled drugs that prescribed by Chinese physicians. The baseline characteristics and clinical parameters of were derived from LANTERN trial for the comparison of IND/GLY and SAL/FLU.¹⁴ The baseline characteristics and clinical parameters were derived from SPARK trial for the comparison of IND/GLY and tiotropium.¹³ The baseline characteristics of cohort patients in this model are listed in [Table 1](#). Clinical model input parameters of different treatment pattern in this model are listed in [Table 2](#).

Lung Function

In the model, lung function improvement is captured as an increase in the actual FEV1 in liters (L) from the clinical trial and converted to a treatment effect versus placebo. We assumed that the lung function benefit occurs at the first 6-month cycle in this model. The FEV1 in liters declined over times and GOLD severity stage of patients updated every cycle in the model. The annual rate of lung function (FEV1) of patients was determined by their age and height by an equation ([Supplementary Materials, Equation 1](#)).^{2,20} Two FEV1 in liters of each patient were updated every cycle as the model was running.

Clinical Events

Different therapies have different effect of avoiding exacerbations and pneumonias. Acute exacerbation of COPD (AECOPD) is defined as acute episodes of breathlessness and sputum production that requiring additional treatment. We used exacerbation and pneumonia ratios, which is exacerbation and pneumonia rates of divided by exacerbation and pneumonia rates of placebo to represent treatment effect of adverse event-avoiding. Background

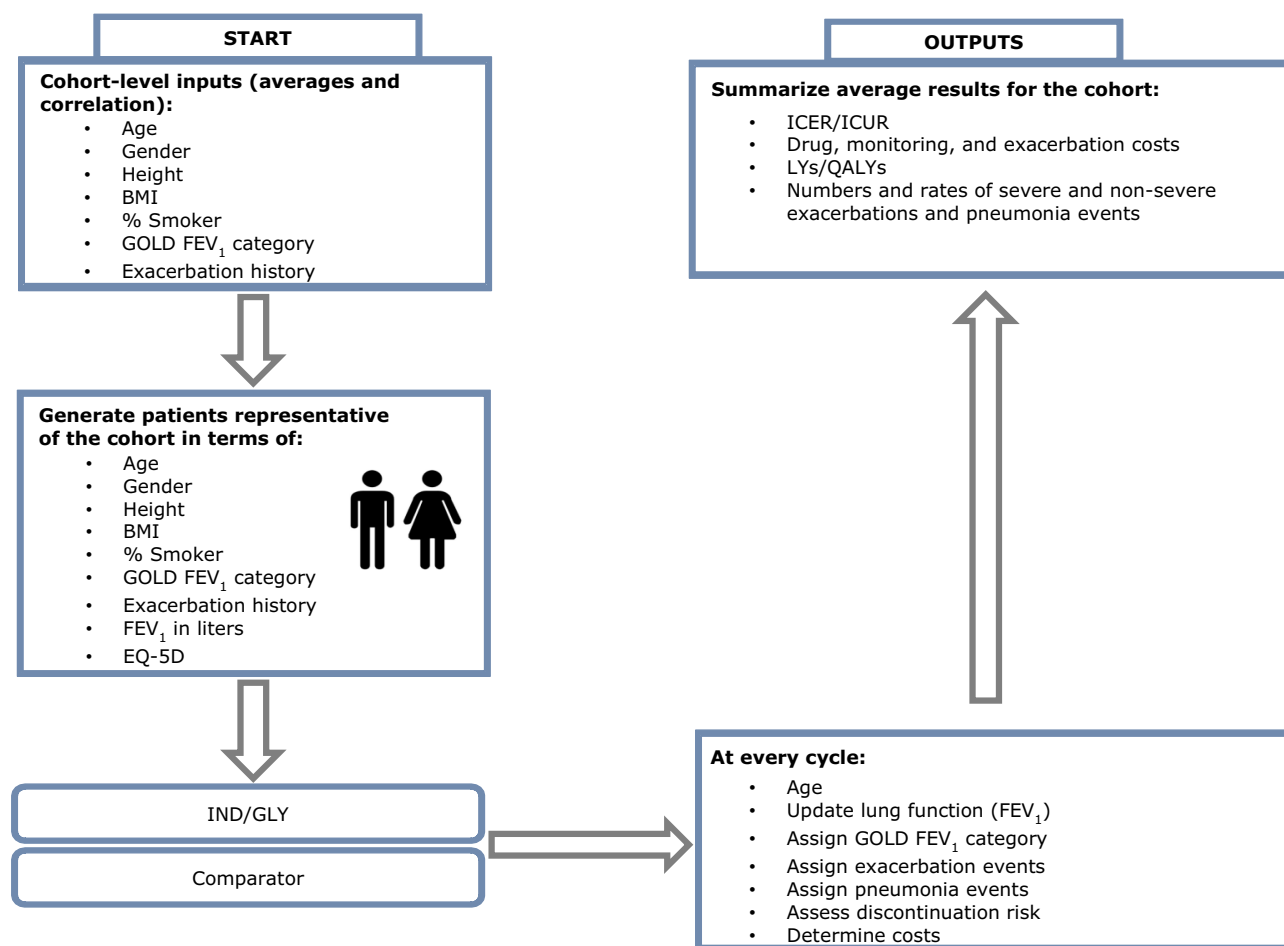


Figure 1 Model structure.

Abbreviations: BMI, body mass index; EQ-5D, EuroQol-Five Dimension; IND/GLY, indacaterol/glycopyrronium; ICER, incremental cost-effectiveness ratio; ICUR, incremental cost-utility ratio; LYs, life years; QALYs, quality-adjusted life years.

exacerbation or pneumonia rates for placebo multiplied by exacerbation ratios of specific treatment pattern come to actual exacerbation or pneumonia rates. Death events occur based on the lifetable of all-cause mortality for normal population in China. A hazard ratio was then applied to this mortality rate as a function of declining FEV₁. For every 10% decline in FEV₁% predicted, there is a 2% increase in mortality risk. Clinical adverse event of acute exacerbation of COPD (AECOPD), pneumonia and death may occur randomly based on the distribution of the ratio of each event at every cycle as model running.

Cost

Drug costs of IND/GLY and comparators were sourced from Health Information System in a tertiary hospital in Beijing, China. Stable period costs and clinical event associated costs were derived from a survey of clinicians from 30 hospitals across the country. Based on their

clinical experience, physicians estimated the costs of stable treatment, acute exacerbation and pneumonia for patients of different levels. In this model, we use the median of physicians' estimated value as parameters.

Model Outcomes

LYs and QALYs were the primary outcomes of different therapy patterns in this model. QALYs is the sum of LYs weighed by health utility of the health state of each LY. Health utility of COPD patients in different health states was calculated based on a published equations ([Supplementary Materials, Equation 2](#)).²¹ The cost effectiveness of IND/GLY versus comparators was determined by calculating incremental total cost per unit effectiveness gained of IND/GLY. We called the ratio of incremental costs and incremental QALYs as incremental cost-utility ratio (ICUR) when we used QALYs as effectiveness. According to standard of WHO, an intervention with

Table 1 Baseline Characteristics of Two Trial Cohort

	LANTERN ¹⁴ (IND/GLY versus SAL/FLU)	SPARK ¹³ (IND/GLY versus Tiotropium)
Age (years)	65.09	63.33
Gender (% male)	91%	75%
Height (cm)	165.69	168.75
BMI (kg/m ²)	23.76	25.29
Current smokers (%)	26%	37%
Exacerbations in previous year	0.21	1.31
GOLD severity		
GOLD I stage	0%	0%
GOLD II stage	53%	0%
GOLD III stage	47%	79%
GOLD IV stage	0%	21%

Abbreviations: IND/GLY, indacaterol/glycopyrronium; SAL/FLU, salmeterol/fluticasone; BMI, body mass index; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

ICUR more than 1–3 times GDP per capita was assumed as cost-effective.²² This threshold to judge cost-effectiveness is so-called willingness-to-pay (WTP). According to the data from the World Bank, the GDP per capita of China in 2019 was 10,261.68 USD, which was equal to 68,617.80 CNY. We selected a lower WTP threshold for chronic diseases like COPD. We used 70,000 CNY as the WTP threshold in this model to assess cost-effectiveness, which is approximate to one-time GDP per capita. All costs and outcomes were discounted as a rate of 3% annually.

Uncertainty Analysis

Both one-way sensitivity analyses (OWSA) and probabilistic sensitivity analyses (PSA) were conducted to evaluate uncertainty of the model results. For OWSA, we adjusted

Table 2 FEV1 in Liters Improvement in Two Cohorts

Items	Mean	Lower CI	Upper CI	Source
FEV1 improvement of LANTERN trial ¹⁴ (L)	IND/GLY: 0.210 SAL/FLU: 0.103	0.121 –0.012	0.299 0.218	14
FEV1 improvement of SPARK trial ¹³ (L)	IND/GLY: 0.190 Tiotropium: 0.130	0.110 0.050	0.270 0.210	13
Background exacerbation rates ¹⁵	Non-severe: 1.010 Severe: 1.010	0.920 0.920	1.340 1.340	15
Exacerbation ratios versus placebo (LANTERN trial) ¹⁴	IND/GLY: 0.450 SAL/FLU: 0.925	0.410 0.500	0.490 1.350	14
Exacerbation ratios versus placebo (SPARK trial) ¹³	IND/GLY: 0.820 Tiotropium: 0.910	0.660 0.730	0.980 1.090	13
Background pneumonia rates	Non-severe: 0.050 Severe: 0.050	0.050 0.050	0.050 0.050	27
Pneumonia ratios versus placebo	IND/GLY: 1.000 SAL/FLU: 3.430 Tiotropium: 1.000	0.900 0.940 1.000	1.100 12.460 1.000	13, 14, 27
Drug cost per day (CNY)	IND/GLY: 8.77 SAL/FLU: 10.00 Tiotropium: 6.00			Survey
Annual stable period cost (CNY)	GOLD I: 1000 GOLD II: 2000 GOLD III: 3000 GOLD IV: 4000			Survey
Exacerbation cost (CNY)	Non-severe: 5000 Severe: 8000			Survey
Pneumonia cost (CNY)	6000			Survey

Abbreviations: IND/GLY, indacaterol/glycopyrronium; SAL/FLU, salmeterol/fluticasone; FEV1, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; CNY, China Yuan.

several individual parameters by $\pm 25\%$ and reassessed the costs and effectiveness of IND/GLY and its comparators while maintaining all other parameters in this model. For the PSA, in which all parameters change spontaneously based on distributions of parameters after 100 iterations. The probability of acceptance of cost-effectiveness of IND/GLY at the willing-to-pay of 70,000CNY was assessed.

Result

IND/GLY versus SAL/FLU

Compared with SAL/FLU, IND/GLY resulted in 0.384 LYs and 0.255 QALYs gained during lifetime simulation. Besides, total cost of IND/GLY was 13,754 CNY lower than SAL/FLU. The incremental cost-effectiveness ratio (ICER) is -35,822 CNY/LY and the ICUR is -53,834 CNY/QALY for IND/GLY versus SAL/FLU. IND/GLY is considered more cost-effective (Table 3).

OWSA showed that FEV1 benefit, exacerbation rate ratio and drug cost sensitively influenced the results in this model. While the results were less sensitive in baseline exacerbation rates. (Supplementary Materials, Table S1) PSA showed that IND/GLY is dominantly cost-effective than SAL/FLU (Figure 2).

Table 3 Results of Whole Life Simulation of IND/GLY vs SAL/FLU

	IND/GLY	SAL/FLU	Incremental
LYs	10.772	10.388	0.384
QALYs	6.762	6.506	0.255
All exacerbations	4.390	6.060	-1.670
Total costs	77,387	91,140	-13,754
Costs/LYs			-35,822
ICUR			-53,834

Abbreviations: IND/GLY, indacaterol/glycopyrronium; SAL/FLU, salmeterol/fluticasone; QALYs, quality-adjusted life years; LYs, life years; ICUR, incremental cost-utility ratio.

IND/GLY versus Tiotropium

Comparing with Tiotropium, IND/GLY resulted in 0.232 LYs and 0.146 QALYs gained during lifetime simulation. The total cost of IND/GLY was 9203 CNY higher than Tiotropium. The ICER is 39,729 CNY/LY and the ICUR is 63,246 CNY/QALY for IND/GLY versus tiotropium. IND/GLY is considered more cost-effective (Table 4).

OWSA showed that FEV1 benefit, exacerbation rate ratio and drug cost sensitively influenced the results in this model. While the results were less sensitive in baseline exacerbation rates. (Supplementary Materials, Table S2)

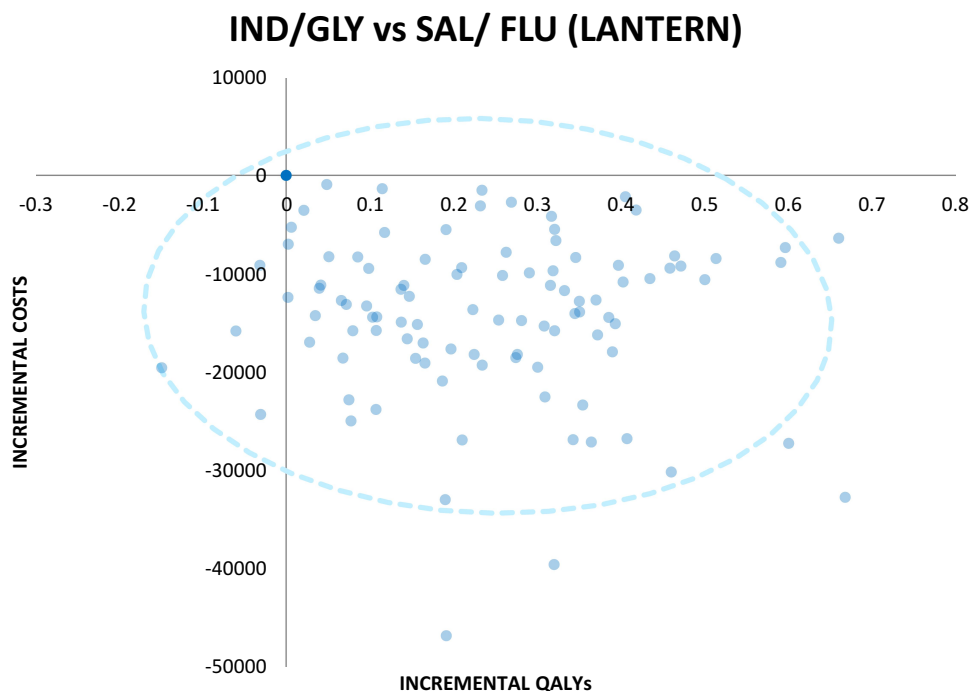


Figure 2 Probability sensitivity analysis of IND/GLY vs SAL/FLU. We showed the results of probability sensitivity analysis (PSA) of IND/GLY vs SAL/FLU in this scatter plot. Each scatter represents an iteration in this model with different incremental costs and QALYs in PSA. This figure showed in most iterations, IND/GLY is with lower costs and longer QALYs than SAL/FLU. We concluded that IND/GLY is with dominate cost-effectiveness than SAL/FLU.

Table 4 Results of Whole Life Simulation of IND/GLY vs Tiotropium

	IND/GLY	Tiotropium	Incremental
LYs	10.712	10.480	0.232
QALYs	6.702	6.556	0.146
All exacerbations	6.400	6.760	-0.360
Total costs	85,730	76,528	11,346
Costs/LYs			39,729
ICUR			63,246

Abbreviations: IND/GLY, indacaterol/glycopyrronium; SAL/FLU, salmeterol/fluticasone; QALYs, quality-adjusted life years; LYs, life years; ICUR, incremental cost-utility ratio.

PSA showed that IND/GLY has 50–60% chance of being cost-effective at the WTP of 70,000 CNY (Figures 3 and 4).

Discussion

In this study, we found that IND/GLY had better clinical effectiveness and lower costs than SAL/FLU. When compared with tiotropium, IND/GLY had better effectiveness and higher costs compared with TIO. Results showed that IND/GLY is moderately cost-effective compared with TIO at the WTP of 70,000 CNY. IND/GLY should be considered as a good option for stable COPD treatment from Chinese payer's perspective.

OWSA showed that factors such as lung function benefits, treatment exacerbation reducing, and drug costs influenced the results sensitively in this model. The evidence that IND/GLY significantly improves lung function and reduces exacerbation compared with single bronchodilator therapies and ICS therapies is valid in previous randomized controlled trials in China and worldwide. The price of novel drugs and interventions are expected to fall further as the market share is growing and because of government–industry negotiation processing in China. Decreasing prices will make IND/GLY more cost-effective. From this we can see that although the results fluctuate sensitively under some scenarios, we can still assume the results of the cost-effectiveness analyses in this model are valid and reliable.

The results of PSA show that IND/GLY is dominantly cost-effective compared with SAL/FLU based on LANTERN trial data. Considering that IND/GLY performed better than SAL/FLU in the LANTERN trial while IND/GLY is at a vlower price than SAL/FLU in the Chinese medical service market, this conclusion is obvious. The results of PSA show that IND/GLY has more than 50% probability to be cost-effective than TIO at the WTP of 70,000CNY (one-time GDP per capita in China) as COPD is a chronic disease. WHO recommend to

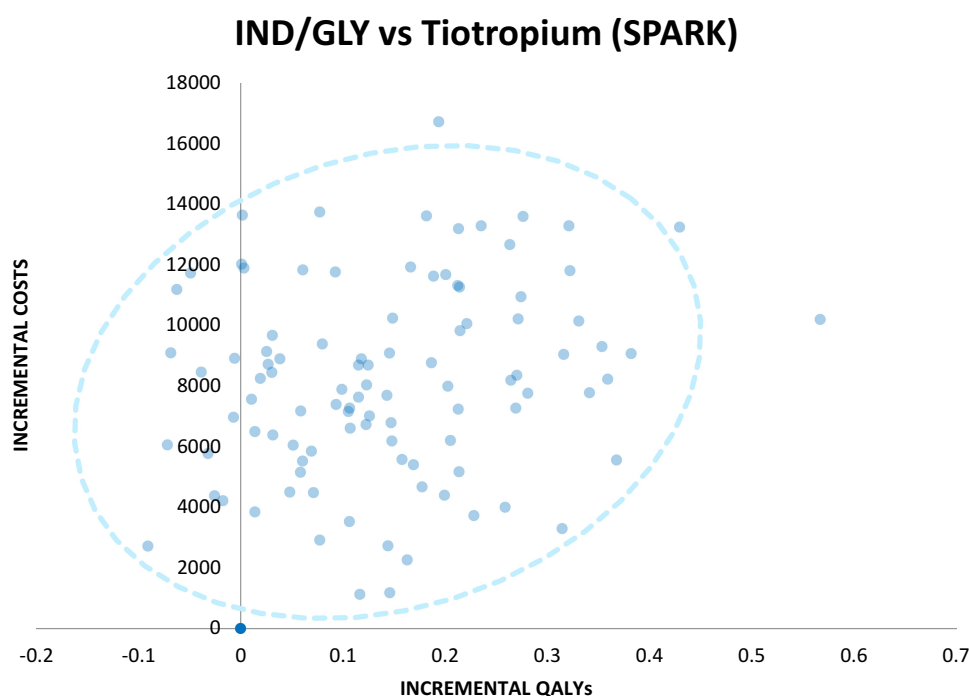


Figure 3 Probability sensitivity analysis of IND/GLY vs tiotropium. We showed the results of probability sensitivity analysis (PSA) of IND/GLY vs tiotropium in this scatter plot. Each scatter represents an iteration in this model with different incremental costs and QALYs in PSA. As IND/GLY can bring longer QALYs but cost more. We need to figure out the probability of scatters to be cost-effective under different threshold.

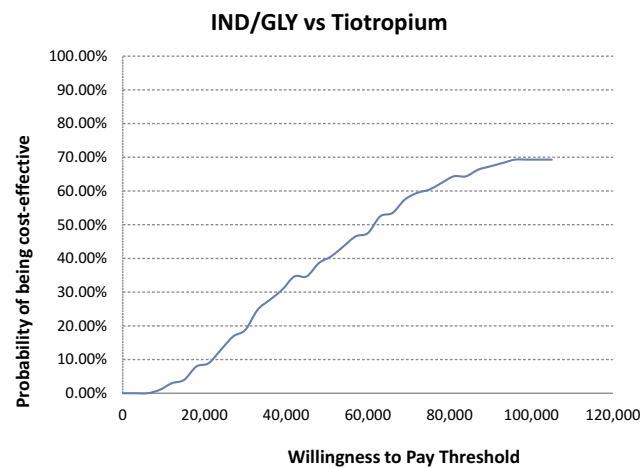


Figure 4 The probability of being cost-effective in PSA of IND/GLY vs tiotropium. This figure showed the probability of iterations in PSA being accepted as cost-effective under different threshold. In our study, we selected 70,000 CNY as willingness-to-pay threshold as we mentioned fully in Method section. We can see the probability of cost-effectiveness of IND/GLY comparing with tiotropium is 50–60%.

use 1–3 times of GDP per capita as WTP in cost-utility analysis.²² If we select a higher WTP, the conclusion of cost-effectiveness of IND/GLY comparing with TIO will be more significant and valid.

In this study, we used a patient-level simulation model to evaluate cost-effectiveness of IND/GLY and comparators. This model can generate and simulate patients randomly from the mean and distribution of each parameter. Compared with the traditional cohort-level Markov model, the patient-level simulation model is more flexible and accurate in simulating patients' health status.²³ As current cost-effectiveness analyses studies of IND/GLY in USA and Europe are based on the cohort-level Markov model,^{17,18} our model-based analysis has more advantages in presenting the health status of COPD patients.

Previous studies have proved the cost-effectiveness of IND/GLY over the comparative treatment in the US and Europe.^{17,18} But there are few studies about cost-effectiveness analyses for IND/GLY from the Chinese payer's perspective. Because China's economic development level, medical service prices, and ethnic composition are completely different from those of Western countries, the cost-effectiveness needs to be re-evaluated. Our study evaluates the cost-effectiveness of IND/GLY using a model with input sourced from clinical trials and China-specific cost data. Our results are valid in the Chinese medical system setting. Since the cost of IND/GLY is lower than SAL/FLU in China, IND/GLY costs less and has better efficacy than SAL/FLU, which is different with previous studies. As the more cost-effective IND/GLY

gradually gains more market share for severe and high-risk COPD in China, the price of SAL/FLU may fall in the future. The cost-effectiveness analyses of IND/GLY comparing with SAL/FLU will require re-evaluation at that time.

Limitations

First, as there is lack of real-world data with long time period of cost and effectiveness of COPD patients with different treatment in China. We did a model-based analysis to simulate real-world situation under Chinese medical system settings. We used a patient-level simulation model as it is more flexible in simulating patients' health status. However, there is still a gap between model simulation and real-world situations. The time duration of clinical trials of COPD treatment is limited. There might be some errors when limited time period trials expanded into model-based whole life simulations. Dual inhaled drugs might be more effective than others in a limited period of time, but there is lack of data on effectiveness beyond the time period of trials. Besides, we may not consider some scenarios as discontinuation of medication, medication for comorbidities, treatment method switches and incorrect inhalations in the model. Considering these dilemmas, there is an urgent need for real-world registry studies to evaluate the effectiveness and cost-effectiveness for COPD patients in China.

Second, costs inputs are derived from a survey over several hospitals. Physicians across China estimate the cost of COPD patients in China from their clinical experience. The results can represent the situation in China in some way, but this may be less reliable than individual-level data, which is hard to get.

Third, the virtual patients in this model were generated from the characteristics of participants of clinical trials. The distribution of parameters may be different from data from epidemiological investigation for COPD in China. Because the effect of clinical trials is limited to subjects of trials with specific demographic characteristics and specific disease severity, the treatment effect for patients with other characteristics and severity is not a direct reference, so it is hard to simulate and evaluate the treatment effectiveness of real patient groups based on data from clinical trials.

Nowadays, triple bronchodilators therapy was proved to effect better than dual bronchodilators therapy for severe COPD treatment.^{24,25} When these new products come into China, we need to assess their value to guide

polycymaking. There is lack of subgroup analyses of cost-effectiveness of IND/GLY. It may perform differently in patients with varying age, sex or disease severity. Besides, as the development of big data, real-world data from health information systems, patient reported outcomes and digital health technology outcomes are more available than before. Considering the limitations of a model-based analyses, future research should focus on comparing the real-world outcomes and the cost-effectiveness of dual bronchodilators in a real-world setting.²⁶

Conclusion

This study found that dual bronchodilator IND/GLY has cost-effectiveness as stable COPD treatment comparing with SAL/FLU and tiotropium under Chinese health care system setting. IND/GLY is acceptable for stable COPD patients in China from Chinese payers' perspective.

Disclosure

The authors report no conflicts of interest in this work.

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