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Dual bronchodilation with indacaterol and tiotropium versus triple therapy, LABA/ICS fixed-dose combinations, and monotherapy in COPD – a network meta-analysis of FEV1 at 12 weeks

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INTRODUCTION

- Chronic obstructive pulmonary disease (COPD) is a disorder characterised by airway obstruction, a decline in lung function, and symptoms such as breathlessness on physical exertion, deteriorating health status, and exacerbations (Bhowmik 2000).
- Effective bronchodilation is a cornerstone of COPD treatment. The GOLD strategy document (GOLD 2011) recommends a long-acting ß-agonist (LABA) in combination with an inhaled corticosteroid (ICS) as a first choice for patients at increased risk of experiencing COPD exacerbations. Triple therapy including a LAMA (a long-acting anticholinergic) + LABA /ICS is recommended as a second choice for such patients. The dual combination of a LABA + LAMA is a second choice option either for patients at increased risk of an exacerbation, or for patients with increased levels of symptoms.
- Dual treatment with indacaterol 150 µg (IND) and tiotropium 18 µg (TIO) combines two effective once daily (OD) bronchodilators. Two randomised controlled trials (RCTs) have been published evaluating IND/TIO versus TIO (Mahler 2012).
- Within the spectrum of treatment options for COPD, clinicians and decision-makers are interested in understanding the efficacy of IND/TIO as a dual bronchodilator in comparison to other dual therapies (LABA/ICS), triple therapies (LABA/ICS/LAMA), and monotherapies. In the absence of direct evidence for these comparisons, a network meta-analysis is of interest to estimate the relative efficacy of these treatments.

OBJECTIVE

- The purpose of this study was to perform a network meta-analysis (NMA) among patients with moderate to severe COPD to evaluate the relative efficacy of IND/TIO in comparison to:
  - Triple therapies (i.e. LAMA plus a fixed dose combination (FDC) of a LABA and ICS):
    - Salmeterol/ fluticasone (50/500µg BID or 50/250µg BID) + tiotropium (18µg OD or 5µg OD) (SAL/FP + TIO)
    - Formoterol/ budesonide (9/160µg BID or 9/320µg BID) + tiotropium (18µg OD or 5µg OD) (FOR/BUD +TIO)
  - Double therapies (LABA/ICS FDC):
    - Salmeterol/ fluticasone (50/500µg BID or 50/250µg BID) (SAL/FP)
    - Formoterol/ budesonide (9/160µg BID or 9/320µg BID) (FOR/BUD)
    - Salmeterol (50µg BID) + tiotropium (18µg OD or 5µg OD) (SAL + TIO)
    - Formoterol (12µg BID) + tiotropium (18µg OD or 5µg OD) (FOR + TIO)
  - Monotherapies:
    - Indacaterol (75µg OD or 150µg OD or 300µg OD), tiotropium (18µg OD or 5µg OD), aclidinium (200µg BID or 400µg BID), salmeterol (50µg BID), formoterol (12µg BID), and placebo
- The outcome of interest was trough forced expiratory volume in 1 second (FEV1)* at 12weeks, which corresponds to the key secondary outcome evaluated for IND/TIO (Mahler 2012).

*In Novartis trials, this outcome was measured at 24 hours post-dose where "trough" reflected the mean of the values assessed at 23 hours 10 minutes and 23 hours 45 minutes following the previous morning dose

METHODS

Evidence base

- In order to identify RCTs concerning the efficacy of the long-acting monotherapies and FDCs for adults with COPD, a systematic literature search was performed.
- MEDLINE® and EMBASE® databases were searched simultaneously for the period of 1989 to July 2011; an additional search of the Cochrane Library clinical trials was also conducted up until 2011. Unpublished Novartis trials were also included which have since been published in 2012.
- As several of the treatment combinations to be compared include ICS as part of the study treatment (i.e. FDCs of LABAs/ICS), the evidence base was restricted to RCTs that did not permit concomitant ICS to ensure placebo patients were sufficiently similar to those in the FDC studies (who did not receive ICS).
- For each of the Novartis trials, subgroup data for *non-ICS* users were included.

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Network meta-analysis (NMA)

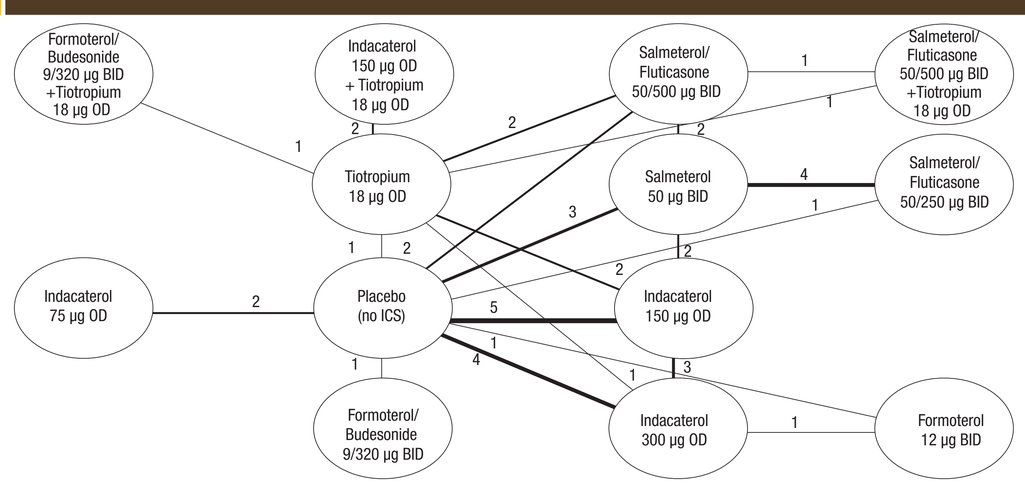
- The efficacy data for trough FEV1 at 12 weeks was analysed simultaneously using a Bayesian NMA. A meta-regression model with a normal likelihood distribution was used (Lu and Ades, 2004; Jansen, 2008; Hoaglin, 2011).
- Fixed and random effects models were compared and selected based on the deviance information criterion (Spiegelhalter 2002).
- Treatment-by-covariate interactions were tested for the following covariates, which were identified as potential treatment-effect modifiers based on clinical expertise: the proportion of current smokers, and the proportion of patients with severe or very severe COPD, and the proportion of males.
- Additional sensitivity analyses were also performed to assess the influence of excluding specific RCTs that differed in terms of specific study or patient characteristics.
- WINBUGS 14.1 statistical software was used for the analyses.

RESULTS

Evidence base

- The systematic literature review identified 23 relevant RCTs. The evidence network is presented in Figure 1. The RCTs were mostly multicentre trials (two were single-centre) and included patients diagnosed with COPD who were 40 years of age or older. Between 50% and 100% were male across the studies and the average age ranged from 61 to 73 years. The proportion of patients with severe or very severe COPD ranged from 23% to 100%.

Figure 1 Network of Evidence



Note: Numbers in the network reflect the number of RCTs available for a specific comparison. RCTs with more than 2 treatment arms provided data for multiple treatment comparisons.
BID, twice daily; OD, once daily

- All RCTs included patients who were current or ex-smokers and specified a smoking history of at least 10 years. However, the proportion of patients who were current smokers across the studies varied (ranging from 0% to 93%), as did the smoking history to a lesser extent (ranging from 34 to 60 pack-years).
- In general, patients were permitted a short-acting beta-agonist as needed (salbutamol or albuterol), although there were some differences in other concomitant medications allowed during the trials (e.g. anticholinergic use during the treatment period). For example, Wouters 2005 allowed long-acting anticholinergics at stable doses during the trial. No RCTs allowed continued use of LABAs during the treatment period.
- The RCTs varied in terms of exacerbation history inclusion criteria: only six of the 23 trials required patients to have experienced at least one exacerbation in the past year (Anzueto 2009, Ferguson 2008, Mansori 2010, Szafranski 2003, Welte 2009, Wouters 2005).
- Based on the results adjusted for current smokers, severity, and sex, smoking status was identified as the most significant potential treatment-effect modifier.
- Given the differences identified across studies in smoking status, use of LAMAs, and exacerbation history, the following analyses were performed:

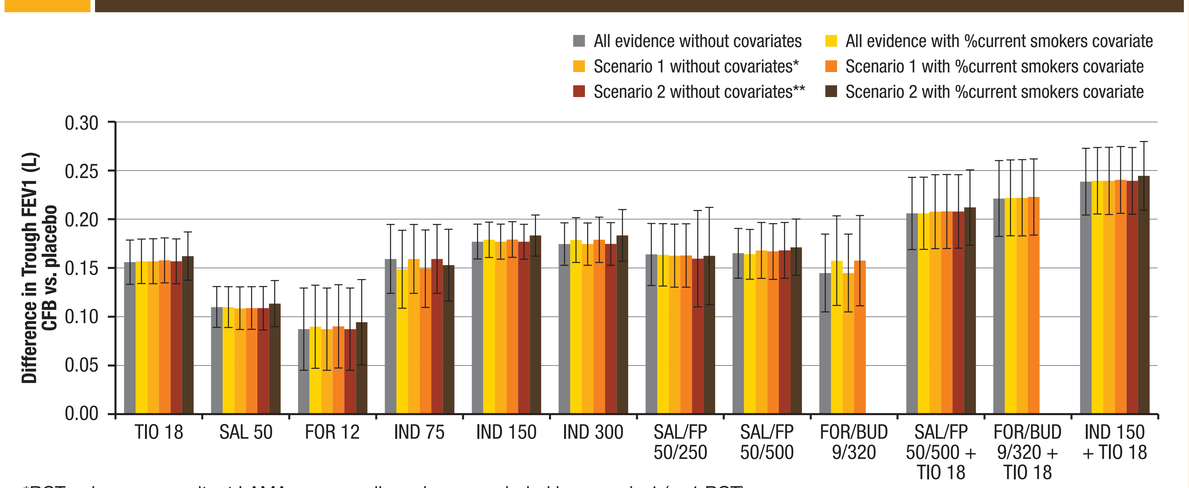
  Base case:
  - All evidence without covariates
  - All evidence with % current smokers covariate

  Scenario analyses:
  - All evidence excluding RCTs that allowed LAMA without covariates
  - All evidence excluding RCTs that allowed LAMA with % current smokers covariate
  - All evidence excluding RCTs that required exacerbation history without covariates
  - All evidence excluding RCTs that required exacerbation history with % current smokers covariate

FEV1 at 12 weeks

- Figure 2 illustrates the results of the NMA in terms of the difference for each active treatment or treatment combination in comparison to placebo for the change from baseline (CFB) in FEV1 at 12 weeks, which demonstrates that results were comparable and did not change substantially when:
  - adjusted for current smokers;
  - RCTs with concomitant anticholinergics were excluded; or
  - RCTs that required an exacerbation history were excluded.
- In the analyses with and without covariates, all active interventions were expected to be more efficacious than placebo.
- Table 1 presents the expected mean trough FEV1 at 12 weeks based on the results of the NMA with and without adjustment for current smokers. The expected rank for each intervention is also presented.
- Figure 3 presents the results of the base case analysis without covariates for IND/TIO in comparison to each intervention with respect to the difference in CFB of trough FEV1 at 12 weeks.

Figure 2 Change from baseline (CFB) in trough FEV1 (Litres) at 12 Weeks – Difference versus placebo and 95% credible interval



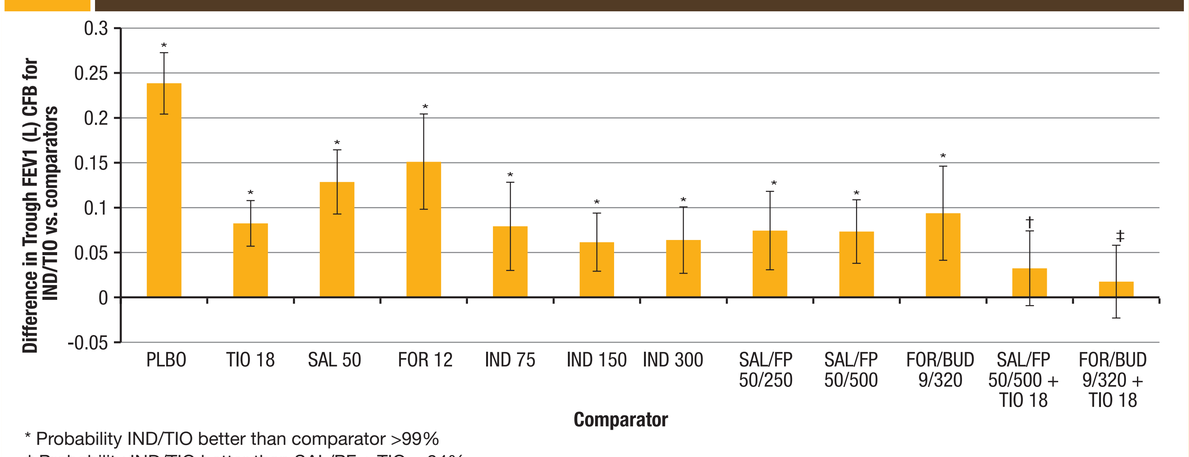
*RCTs where concomitant LAMA use was allowed were excluded in scenario 1 (n=1 RCT);
**RCTs which required an exacerbation history were excluded in scenario 2 (n=6 RCTs); thereby no RCTs which evaluated FOR/BUD or FOR/BUD + TIO were included in scenario 2.

Table 1 Expected LS Mean Trough FEV1 (Litres) at 12 Weeks per Intervention, Probability of Intervention being Best and Worst, and Expected Ranking

Intervention	Without adjustment for covariates		With adjustment for current smokers	
	Expected mean and 95% CrI	Rank	Expected mean and 95% CrI	Rank
PLBO	1.26 (1.24, 1.28)	13	1.26 (1.24, 1.28)	13
TIO 18	1.41 (1.38, 1.44)	8	1.41 (1.38, 1.44)	8
SAL 50	1.37 (1.34, 1.39)	11	1.37 (1.34, 1.39)	11
FOR 12	1.34 (1.3, 1.39)	12	1.35 (1.3, 1.39)	12
IND 75	1.42 (1.38, 1.46)	8	1.41 (1.36, 1.45)	10
IND 150	1.43 (1.41, 1.46)	4	1.44 (1.41, 1.46)	4
IND 300	1.43 (1.4, 1.46)	4	1.44 (1.41, 1.47)	4
SAL/FP 50/250	1.42 (1.38, 1.46)	6	1.42 (1.38, 1.46)	6
SAL/FP 50/500	1.42 (1.39, 1.45)	6	1.42 (1.39, 1.45)	6
FOR/BUD 9/320	1.40 (1.36, 1.45)	10	1.41 (1.37, 1.46)	8
SAL/FP 50/500 + TIO 18	1.46 (1.42, 1.50)	3	1.46 (1.42, 1.50)	3
FOR/BUD 9/320 + TIO 18	1.48 (1.44, 1.52)	2	1.48 (1.44, 1.52)	2
IND 150 + TIO 18	1.50 (1.46, 1.53)	1	1.50 (1.46, 1.54)	1

CrI, credible interval

Figure 3 Change from Baseline (CFB) in Trough FEV1 at 12 Weeks – Difference IND/TIO Versus Comparator and 95% Credible Interval



* Probability IND/TIO better than comparator >99%
† Probability IND/TIO better than SAL/PF + TIO = 94%
‡ Probability IND/TIO better than FOR/BUD + TIO = 80%

- In comparison to placebo, IND/TIO resulted in a higher CFB than placebo by 0.24L (95%CrI: 0.20L, 0.27L).
- In comparison to the triple therapies (i.e. FDCs in combination with TIO), IND/TIO was likely to be favourable versus SAL/FP 50/500µg + TIO 18µg [difference 0.03L (95%CrI: -0.01L, 0.07L); probability better: 94%] and comparable to FOR/BUD 9/320µg + TIO 18µg [difference 0.02L (95%CrI: -0.02L, 0.06L); probability better: 80%].
- In comparison to FDCs alone, IND/TIO resulted in a higher CFB with an advantage ranging from 0.07L (95%CrI: 0.03L, 0.12L) to 0.09L (95%CrI: 0.04L, 0.15L).
- In comparison to the monotherapies assessed, IND/TIO also resulted in a higher change from baseline.
- Out of the 13 regimens evaluated, there is a 77% probability that IND/TIO was the most efficacious treatment in terms of CFB in FEV1 at 12 weeks.

DISCUSSION

- The main objective of this study was to compare the efficacy of IND/TIO OD versus FDCs in combination with TIO, versus FDCs alone, or versus individual bronchodilators.
- In terms of FEV1 at 12 weeks, IND/TIO was expected to be comparable to the triple therapies of FDCs plus TIO. Furthermore, the results indicate that IND/TIO was more efficacious than FDCs alone and bronchodilators alone.
- Some monotherapy bronchodilators showed a better point estimate for expected trough FEV1 at 12 weeks than the LABA/ICS FDCs.
- If the trials differ among the direct comparisons regarding study and patient characteristics, and these differences are modifiers of the relative treatment effects, then the estimate of the indirect and mixed comparisons is biased (Cooper, 2009; Jansen, 2011).
- To avoid biased estimates, meta-regression models were used which incorporated smoking status as a covariate and additionally, some differences were explored by excluding specific studies. These sensitivity analyses led to similar results, suggesting that results were not likely to be affected by similarity or consistency violations. However, it was not possible to assess the similarity of the studies in terms of all patient characteristics and it has to be accepted that there is the risk of residual confounding bias given this analysis was based on study-level data.

CONCLUSIONS

- Overall, results of the NMA suggest that in terms of FEV1 at 12 weeks, dual bronchodilation with IND/TIO was comparable to triple therapy (LABA/ICS FDCs in combination with TIO), more efficacious than LABA/ICS FDCs alone, and more efficacious than the alternative monotherapies among patients with moderate to severe COPD.

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