

RAPID APPRAISAL

Name of Trial: Tiotropium in combination with placebo, salmeterol or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease. A randomised trial.

Reference: Aaron SD, Vandemheen KL, Fergusson D et al. *Ann Intern Med*: 2007;146; **Early on-line publication** (<http://www.annals.org/cgi/content/full/0000605-200704170-00152v1>)

Question: Does combining tiotropium with salmeterol or salmeterol plus fluticasone reduce the number of exacerbations experienced by patients with moderate to severe COPD, when compared with tiotropium and placebo?

Summary: The data from this small single-centre study do not show any significant difference in the proportion of patients experiencing one or more exacerbations when treated with a combination of tiotropium/salmeterol/fluticasone compared with tiotropium/placebo. The proportion of patients who experienced at least one exacerbation over the 52-week study period did not significantly differ between the tiotropium/placebo and tiotropium/salmeterol/fluticasone groups (62.8% and 60.0% respectively). The data from this trial do not provide evidence to support the use of triple therapy (tiotropium/salmeterol/fluticasone) in patients with moderate to severe COPD experiencing one or more exacerbations per year.

Did the study ask a clearly focussed question?

Yes – The study aimed to determine whether combining tiotropium with salmeterol or salmeterol/fluticasone improved clinical outcomes in adults with moderate to severe chronic obstructive pulmonary disease (COPD).¹ The primary end point of this trial was the proportion of patients experiencing one or more exacerbations requiring treatment with systemic corticosteroids or antibiotics during the study period (52 weeks). Secondary outcomes were the mean number of COPD exacerbations per patient-year, the total number of exacerbations that resulted in urgent visits to a healthcare provider or emergency department, hospitalisations including those that were COPD-related, changes in health-related quality of life, dyspnoea and lung function.

Was the study design appropriate?

Yes – The study was a prospective, double-blind, placebo-controlled, randomised, parallel-group study. Eligible patients were over 35 years of age with a history of ≥ 10 pack-years of cigarette smoking, documented airflow obstruction with an FEV₁/FVC ratio < 0.7 and a post bronchodilator FEV₁ $< 65\%$ predicted. Patients enrolled in this study also had to have experienced one or more exacerbations requiring treatment with systemic steroids or antibiotics in the last 12 months. Patients were randomly allocated to one of three treatment arms for 52 weeks;

- tiotropium 18 micrograms once daily plus placebo inhaler two puffs twice daily (n = 156) **T/P**.

- tiotropium 18 micrograms once daily plus salmeterol 25 micrograms two puffs twice daily (n = 148) **T/S**.
- tiotropium 18 micrograms once daily plus salmeterol 25 micrograms / fluticasone 250 micrograms two puffs twice daily (n = 145) **T/S/F**.

All patients were supplied with a short acting beta₂ agonist inhaler and instructed to use it when necessary to relieve symptoms. All treatment with inhaled corticosteroids, long-acting beta₂ agonists and anticholinergics was discontinued prior to inclusion in the study. The study was not funded by the pharmaceutical industry.

Were participants appropriately allocated to intervention and control groups?

Yes – Randomisation was conducted through a computer generated allocation system blocked in variables of 9 or 12 and stratified by site. Differences in baseline characteristics included the percentage of current smokers (27% in the T/P group, 24% in the T/S group and 32% in the T/S/F group), patients with congestive heart failure (4%, 1% and 4%, respectively) and cancer (6%, 10% and 7%, respectively). Differences in medication use prior to inclusion in the study were: tiotropium (58%, 56% and 46%, respectively), ipratropium (34%, 45% and 43%, respectively), inhaled corticosteroids (25%, 35% and 27%, respectively) and methylxanthines (7%, 12% and 6%, respectively).

Were participants, staff and study personnel 'blind' to participants study group?

Yes – Neither research staff nor patients were aware of the treatment assignment before or after

randomisation. A blinded adjudication committee reviewed all reports of suspected COPD exacerbations to ensure each episode fitted the study definition.

Were all of the participants who entered into the trial accounted for at its conclusion?

Yes – The final analysis was conducted on an intention-to-treat basis. Initially 451 randomisation numbers were allocated; however, two patients were withdrawn at this stage and who received no study medication. Therefore, 449 patients were randomised to treatment. Premature discontinuation of study medication occurred in 39% of the study population. Of these patients, 69% went on to receive open-label treatment with a combination inhaler, containing inhaled corticosteroid and long-acting beta agonist, for the remainder of the study (T/P group = 55/74, T/S group = 45/64 and T/S/F group = 20/37).

Were the participants in all groups followed up and data collected in the same way?

Yes – Patients were monitored for exacerbations by monthly telephone calls and subsequent information gathered from healthcare professionals involved in each episode. All study outcomes were assessed through patient visits at baseline and 4, 20, 36 and 52 weeks. Patients were followed-up for the full 52 weeks irrespective of whether or not they had experienced an exacerbation or discontinued treatment. Study blinding was not broken for patients who prematurely discontinued study treatment.

Was the study large enough?

Yes – With 130 patients in each treatment arm this study had 80% power to detect an 18% difference in risk of exacerbation with an alpha value of 0.05. This assumed a 55% baseline risk of exacerbation. To allow for a 5% dropout rate a sample size of 144 patients per arm, or 432 patients in total, was required.

The study was neither designed nor of sufficient power to compare differences between the T/S and T/S/F treatment arms.

How are the results presented and what are the main results?

Primary endpoint:

The proportions of patients who experienced at least one exacerbation over the 52-week study period did not significantly differ among the T/P group and the T/S and T/S/F groups (62.8%, 64.8% and 60.0% respectively). The unadjusted odds ratio of an exacerbation was 1.03 (95%CI, 0.63 to 1.67) with T/S versus T/P and 0.85 (95%

CI, 0.52 to 1.38) for T/S/F compared with T/P. Adjustment for site, age, sex, severity of airflow obstruction at baseline, medication and home oxygen use before entering study, current smoking status and comorbid illness did not appreciably change the results; the non-significant differences were maintained.

Secondary endpoints:

The investigators also reported no significant differences in the mean number of exacerbations per year, time to first exacerbation and level of dyspnoea. Each of the treatment groups demonstrated a clinically significant improvement in health-related quality of life after one year of treatment, with the largest improvement seen in the T/S/F group (-8.6 points, $p = 0.01$ compared with T/P). Improvements in lung function were measured using pre-bronchodilator FEV₁ (an increase of 86 ml in the T/S/F group compared with 27 ml in the T/P group, $p = 0.049$) and percentage FEV₁ predicted (4.6% in the T/S/F group compared with 1.3% in the T/P group, $p = 0.005$). Changes in lung function and health-related quality of life could also have been influenced by patients starting pulmonary rehabilitation (7%), stopping smoking (3%) and starting home oxygen (5%).

No significant difference was seen in the number of urgent physician or emergency department visits for COPD exacerbations, whereas the T/S/F treatment arm demonstrated fewer COPD-related hospitalisations (rate ratio = 0.53, 95%CI 0.33 to 0.86 compared with T/P, $p = 0.01$).

How precise are the results?

This was a small, randomised controlled trial where more than 40% of patients in the T/P and T/S groups discontinued treatment prior to the end of the study period.

How safe were the regimens?

There were 16 deaths overall in the study population. Of these four occurred in the T/P group (2.6%), six in the T/S group (4.1%) and six in the T/S/F group (4.1%) no data on the causes of death were supplied. Adverse events occurred in 23.7%, 21.6% and 30.3% of the treatment groups respectively. There was a higher incidence of adverse events associated with inhaled corticosteroid use in the T/S/F group (dry or sore mouth, oral candidiasis and voice hoarseness) compared with the T/P and T/S groups. Treatment with tiotropium and placebo was also associated with a higher incidence of respiratory failure leading to mechanical ventilation or death (4.5% compared with 2.0% in the T/S group and 1.4% in the T/S/F group).

Can the results be applied to the local population?

This study was conducted in Canadian patients with moderate to severe COPD with a mean FEV₁ of 39% predicted. At baseline 47% of the patient population in this trial were being treated with a combination of ICS and LABA. NICE recommends that a long-acting bronchodilator should be considered when symptoms are not controlled using short-acting agents or where patients are experiencing frequent exacerbations (two or more in a 12 month period).² A four week trial of treatment with an inhaled corticosteroid is also recommended for patients with an FEV₁ ≤ 50% experiencing two or more exacerbations in the preceding 12 months.² The inclusion criteria for this trial do not fit with these recommendations. Baseline exacerbation frequency was not reported in this trial therefore it is not possible to determine what proportion of patients within the trial fit these criteria. In addition, patients in this trial were closely monitored which is likely to have improved their

compliance with treatment, therefore the results may not be achievable under normal conditions.

Does treatment with a combination of tiotropium, salmeterol and fluticasone reduce the exacerbation rate in patients with moderate to severe chronic obstructive pulmonary disease compared with tiotropium alone?

No - The data from this trial do not provide evidence to support the use of triple therapy in patients with moderate to severe COPD experiencing one or more exacerbations per year. No significant difference in the number of exacerbations experienced by patients receiving triple therapy (tiotropium/salmeterol/and fluticasone), compared with tiotropium/placebo therapy, could be demonstrated. Treatment with ICS and a long-acting bronchodilator should be reserved for patients with an FEV₁ ≤ 50%, two or more exacerbations in the preceding 12 months and symptoms that are not controlled with short-acting bronchodilators.

REFERENCES

1. Aaron SD, Vandemheen KL, Fergusson D et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease. Ann Intern Med 2007;146. Early on-line publication (<http://www.annals.org/cgi/content/full/0000605-200704170-00152v1>)
2. National Institute for Health and Clinical Excellence. Management of chronic obstructive pulmonary disease in adults in primary and secondary care. Clinical Guideline 12; February 2004.

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