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JOURNAL ROUND-UP

Lung volume reduction surgery vs medical therapy for severe emphysema

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Naunheim KS *et al*. Long-term follow-up of patients receiving lung volume reduction surgery versus medical therapy for severe emphysema, by the National Emphysema Treatment Trial Research Group. *Ann Thorac Surg* 2006;82:431-443.

The National Emphysema Treatment Trial defined subgroups of patients with severe emphysema in whom lung volume reduction surgery (LVRS) improved survival and function at two years. 1218 patients were randomised to receive either LVRS or medical management for their severe emphysema. This extension study provides follow-up data on these patients for at least a further two years after the initial trial.

Overall, the 5-year risk ratio (RR) for death was 0.86 (p= 0.02) in the LVRS group as compared to medical therapy. Maximal exercise was better through three years and health-related quality of life (as assessed by the SGRQ) was better through four years in the LVRS group overall.

Analysis of data for the four subgroups showed that the differences between them remained. The upper lobe patients with low exercise capacity demonstrated better survival at five years (p=0.003), better maximal exercise through three years (p<0.001) and less symptoms through five years (p=0.01 at five years). Lower lobe predominant disease showed poorer survival compared to upper lobe disease. Upper lobe disease with high exercise tolerance did not show a survival benefit, but did show an improved exercise capacity (p<0.01, years 1 to 3) and health-related quality of life (p<0.01, years 1 to 4).

Conclusions: The beneficial effects of LVRS lasted beyond the two years of the first trial to almost five years. LVRS can be recommended for upper lobe-predominant emphysema patients with low exercise capacity because it gives a symptom and survival advantage. In those with upper lobe emphysema and high exercise capacity, LVRS will not confer a survival advantage, but may help symptoms.

Comment

This is an interesting study giving follow-up data from the initial national emphysema trial. It shows us that we should remember about LVRS as a treatment for emphysema in the right subset of patients – i.e. patients with large upper lobe bullae who are disabled because of poor exercise capacity. The surgical techniques are being revised and now include an endobronchial approach, which may make future results of LVRS even more favorable. Surgical treatment and even partial cure for severe emphysema is a real option in some patients.

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Effects of tiotropium combined with either salmeterol or salmeterol/fluticasone in moderate to severe COPD

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Aaron SD *et al*. Tiotropium in combination with placebo, salmeterol, or fluticasone–salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2007;146(8):545-55.

This randomised double-blind placebo-controlled study ran from October 2003 until January 2006 in 27 centres across Canada and involved 449 patients with moderate or severe COPD. The intervention was one year of tiotropium with either placebo, salmeterol 25 mcg two puffs twice-daily, or fluticasone/salmeterol 250/25 two puffs twice-daily. The objective was to determine whether combining tiotropium with salmeterol or fluticasone/salmeterol improves clinical outcomes in adults with moderate to severe COPD compared with tiotropium alone.

Eligible patients had to have had at least one exacerbation of COPD requiring treatment with systemic steroids or antibiotics within the 12 months before randomisation. Additional inclusion criteria were: age older than 35 years; a history of 10 pack-years or more of cigarette smoking; and documented chronic airflow obstruction with an FEV_1/FVC ratio less than 0.70 and a post-bronchodilator FEV_1 less than

65% predicted.

Exclusions included: asthma; congestive heart failure; oral prednisone treatment; intolerance to any of the study drugs; a severe exacerbation within the 28 days prior to study entry; glaucoma; severe urinary tract obstruction; lung volume reduction surgery or transplant; bronchiectasis; and pregnancy or breastfeeding.

The primary outcome was the proportion of patients in each treatment group who experienced a COPD exacerbation within 52 weeks of randomisation. Respiratory exacerbations were defined according to the 2000 Aspen Lung Conference Consensus definition as, "a sustained worsening of the patient's respiratory condition, from the stable state and beyond normal day-to-day variations, necessitating a change in regular medication in a patient with underlying COPD". An acute change in regular COPD medications was defined as physician-directed short-term use of oral or intravenous steroids, oral or intravenous antibiotics, or both therapies.

Secondary outcomes were: the mean number of COPD exacerbations per patient-year; the total number of exacerbations that resulted in urgent visits to a health care provider or emergency department; the number of hospitalisations for COPD; the total number of hospitalisations for all causes; and changes in health-related quality of life (measured by the St George's Respiratory Questionaire, SGRQ), dyspnoea (TDI), and lung function (FEV_1).

Funding Sources: The Canadian Institutes of Health Research and The Ontario Thoracic Society provided peer-reviewed funding for this study. There was no pharmaceutical company funding.

Results: The addition of fluticasone/salmeterol or salmeterol to tiotropium did not reduce the proportion of patients who experienced one or more COPD exacerbations during 1 year. The addition of fluticasone/salmeterol to tiotropium resulted in a non-significant 2.8% absolute reduction [CI, –8.2 to 13.8 percentage points] in the percentage of patients who experienced at least one exacerbation during 1 year.

The combination did improve a number of secondary outcomes. The hospitalisation rate for COPD exacerbations, and all-cause hospitalisation rate, was statistically lower in patients who received tiotropium plus fluticasone/salmeterol versus those who received tiotropium plus placebo – incidence rate ratio 0.53 [CI, 0.33 to 0.86] for the combination compared to tiotropium alone for COPD hospitalisation, and incidence rate ratio 0.67 [CI, 0.45 to 0.99] for all-cause hospitalisation. In contrast, tiotropium plus salmeterol did not statistically improve lung function or hospitalisation rates compared with tiotropium plus placebo. Health-related quality of life (p=0.01) – as measured by the SGRQ – and lung function (p= 0.049) were also improved by the addition of fluticasone/salmeterol to tiotropium therapy.

The median time to first exacerbation was 130 days in the tiotropium plus placebo group, 128 days in the tiotropium plus salmeterol group, and 217 days in the tiotropium plus fluticasone/salmeterol group. This did not meet statistical significance as the adjusted hazard ratio was 0.80 (CI, 0.60 to 1.08; p=0.15). There was also no difference in mortality or serious adverse events in the three groups.

Conclusion: The addition of fluticasone/salmeterol to tiotropium may improve lung function and quality of life, while decreasing hospitalisations, but it does not seem to affect numbers of exacerbations in patients with moderate or severe COPD.

Comment

This study seems to fly against the weight of previous evidence that inhaled corticosteroids (ICS) would reduce exacerbations in patients with moderate to severe COPD. But is this really the case?

Firstly, more than 40% of patients who received tiotropium plus placebo and tiotropium plus salmeterol discontinued therapy prematurely, and many crossed over to treatment with open-label ICS or long-acting beta-agonists (LABAs). This would tend to underestimate exacerbations in the placebo group who ended up getting treatment once withdrawn.

Secondly, as the effect on exacerbations was modest, the study may have been underpowered to show the appropriate change in only one year.

Thirdly, the FEV_1 entry criterion was < 65% predicted, a higher level of lung function than the entry criterion in many previous studies assessing the role of ICS in COPD. Is the effect of ICS occurring only in more severe disease?

The impression therefore is that although the addition of fluticasone/salmeterol to tiotropium did not affect overall exacerbation rates, combined therapy with tiotropium plus fluticasone/salmeterol may well modify exacerbation severity, so that these patients are less likely to require hospitalisation for their COPD exacerbation. The same was not true of salmeterol alone. Total exacerbation rates in the study group are likely to have been affected by the high drop out rate. Improvement in lung function and quality of life are valid secondary outcomes. The TORCH study[1] showed a decrease in exacerbations in COPD patients with an FEV_1 of less than 60%, but they were not otherwise treated with a LABA. Again, there was no definite statistical effect on mortality in this study, similar to the TORCH study results.

The message for clinicians is that COPD patients with an FEV_1 of less than 65% predicted who are on treatment with tiotropium and who are having exacerbations should be put

on additional salmeterol/fluticasone at a dose of 50/500 twice-daily to help prevent further exacerbations and to improve quality of life. This message should NOT be extrapolated to those patients with better lung function or those not having exacerbations; these patients will still do better with LABA compared to short-acting bronchodilators alone. ICS are not without side effects and we still must measure the risk-benefit ratio of ICS in patient groups where benefit has not been proven.

Reference

1. Calverley PM, Anderson JA, Celli B *et al;* TORCH investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;**356**:775-89.

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