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The Addition of Tiotropium in Uncontrolled Asthma

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Abstract

- Many patients with asthma have poorly controlled disease despite the use of both an inhaled corticosteroid (ICS) and a long acting beta agonist (LABA).
- The review explored several studies that compared the addition of tiotropium to patients with uncontrolled asthma currently using both a ICA and a LABA to determine if further symptom reduction is obtained along with reduction of exacerbations
- It was found that patients with poorly controlled asthma will benefit from the addition of tiotropium to the current medication regimen of an ICS and a LABA. Tiotropium offers providers an additional disease controlling option in cases where treatment is already limited.

Introduction

- For some adults with asthma, symptom relief is inadequate when receiving treatment with an ICS and a LABA. Besides increasing the amount of steroid to a maximum dose, which comes with increased side effects, there has been no other alternative.
- Recently it has come into question whether or not the addition of anticholinergic agents such as tiotropium would be useful addition to asthma patients who remain symptomatic despite max therapy.

Statement of the Problem

- Asthma has become a worldwide epidemic. Further research ad therapy needs to be initiated to reduce morbidity and mortality in those patients already on maximum recommended drug regimen.

Research Question

- In adult patients with uncontrolled asthma using maximum doses of both ICS and a LABA, will the addition of tiotropium improve lung function and reduce the number of asthma related exacerbations?
- Is tiotropium safe and efficacious?
- Is tiotropium cost effective compared to other therapeutics?

Literature Review

- The search of Literature identified the main points:
- Kerstjens (2012) found that at 24 weeks the peak FEV_1 with the addition of tiotropium, increased slightly (P=0.01), and the time to first exacerbation was increased by 56 days (P=0.03)
- Peters (2010) found that those patients receiving tiotropium had a morning PEF that was 25.8L/min higher than those patients receiving a double dose of glucocorticoid (P=<0.001).
- Tang (2013) found improvements in trough FEV_1 at 4 weeks (P<0.0001), 24 weeks (P<0.0001) and 48 weeks (P<0.0001) in the tiotropium group versus placebo.
- In a systematic review by Kesten (2009), tiotropium showed no increased risk for cardiac or vascular events when compared to placebo.
- A cost analysis by Hoogendoorn (2012), found tiotropium was more expensive when compared to salmeterol, but had lower overall costs when exacerbations were taken into effect.
- Dalal (2010) found that unadjusted mean costs of treatment with fluticasone/salmeterol ($2018) was lower when compared with tiotropium ($2453).

Applicability to Clinical Practice

- Tiotropium may have a place in clinical practice for those patients with uncontrolled asthma already on max therapy with an ICS and a LABA, as the small improvements in lung function will benefit this group in the long run.
- However, tiotropium most likely does not have a place in clinical practice for those patients who have symptom control.

Discussion

Table 3 Total 1-yr costs per patient after imputation and bootstrapping, trial-based analysis

	Tiotropium	Salmeterol	Difference
SHI perspective			
Study medication	581	369	213
Exacerbation-related healthcare use#	363 (317–411)	450 (400–502)	-87 (-157–-19)
Other COPD medication	144 (140–149)	144 (139–149)	1 (-6-7)
Total	1089 (1041–1137)	963 (912–1016)	126 (55–195)
Societal perspective			
Study medication	736	420	316
Exacerbation-related healthcare use#	363 (317–411)	450 (400–502)	-87 (-157–-19)
Other COPD medication	170 (164–176)	170 (164–176)	1 (-7-9)
Paid by the patient¶	24 (22–27)	29 (26–32)	-5 (-9–-1)
Productivity loss	115 (92–139)	170 (140–201)	-55 (-94–-18)
Total	1409 (1349–1469)	1239 (1171–1310)	170 (77–260)

Costs are presented as 2010 €. Data are presented as n or mean (95% uncertainty interval). SHI: statutory health insurance; COPD: chronic obstructive pulmonary disease. #: includes costs of hospital admissions, ambulance rides, visits to the emergency room and outpatient contacts to healthcare providers; ¶: includes patient co-payments for hospitalisation, ambulance rides, contacts with healthcare providers and travel costs.

Taken from "Cost-effectiveness of tiotropium versus salmeterol: the POET-COPD trial," by M. Hoogendoorn, M.J. Al, K. Beeh, D. Bowles, J. Matthias Graf von der Schulenburg, J. Lungershausen, B.U. Monz, H. Schmidt, C. Vogelmeier, M. Rutten-van Molken, 2012,*Europen Respiratory Journal*, 41 (3), p.560.

Discussion

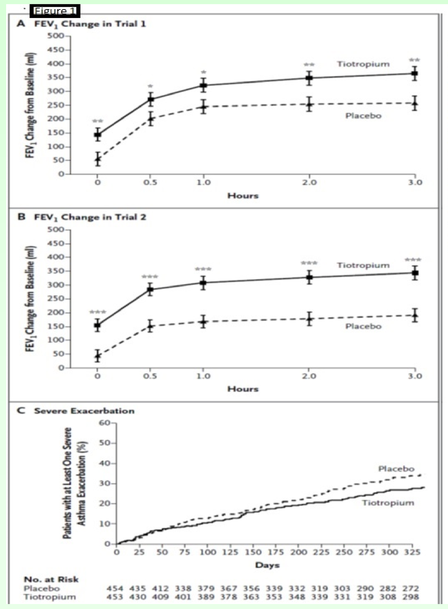

Figure 1-The mean changes in lung function from baseline to 24 weeks, as measured by the FEV1 for 3 hours after the administration of the study and maintenance drugs, are shown for trial 1 (Panel A) and trial 2 (Panel B). Panel C shows the cumulative number of severe exacerbaions.

Taken from "Tiotropium in Asthma Poorly Controlled with Standard Combination Therapy," by H.A.M. Kerstjens, M. Engel, R. Dahl, P. Paggiaro, E. Beck, M. Vandewalker, R. Sigmund, W. Seibold, P. Moronic-Zentgraf, E. Bateman, 2012, *The New England Journal of Medicine*, 367, p. 1204

Table 1 Mean Difference between Tiotropium and Placebo in the Change from Baseline to Week 24 and Week 48 in the Two Trials.*

Measure and Week	Trial 1		Trial 2	
	No. of Patients	Difference in Change *mean (95% CI)*	No. of Patients	Difference in Change *mean (95% CI)*
Forced expiratory volume in 1 sec				
Peak at 0–3 hr (ml)				
24 wk†	428	86 (20 to 152)‡	423	154 (91 to 217)§
48 wk	417	73 (5 to 140)‡	403	152 (87 to 217)§
Trough (ml)				
24 wk†	428	88 (27 to 149)¶	422	111 (53 to 169)§
48 wk	417	42 (–21 to 104)	402	92 (32 to 151)¶
Forced vital capacity				
Peak (ml)				
24 wk	428	89 (6 to 173)‡	423	94 (10 to 177)‡
48 wk	417	125 (40 to 210)¶	403	114 (29 to 200)¶
Trough (ml)				
24 wk	428	136 (58 to 214)§	422	106 (25 to 186)¶
48 wk	417	111 (31 to 190)¶	402	71 (–12 to 153)
Peak expiratory flow‖				
Morning (liters/min)				
24 wk	414	21.5 (12.7 to 30.4)§	407	23.3 (14.5 to 32.1)§
48 wk	369	20.3 (11.3 to 29.4)§	378	14.0 (5.1 to 22.9)¶
Evening (liters/min)				
24 wk	413	22.0 (13.0 to 30.9)§	405	29.9 (20.7 to 39.1)§
48 wk	369	22.6 (13.5 to 31.7)§	377	24.5 (15.1 to 33.8)§

* All differences are calculated as the adjusted mean change from baseline, as measured at randomization (visit 2), for tiotropium minus placebo. Baseline was defined as the measurement obtained before any study or maintenance medication was administered. Values for forced expiratory volume in 1 second and forced vital capacity have been adjusted for treatment, center, visit, baseline value, and interactions between treatment and visit and between baseline value and visit.
† This category was a coprimary end point in the two trials.
‡ P<0.05.
§ P<0.001.
¶ P<0.01.
‖ All values are means of weekly measurements of peak expiratory flow.

Taken from "Tiotropium in Asthma Poorly Controlled with Standard Combination Therapy," by H.A.M. Kerstjens, M. Engel, R. Dahl, P. Paggiaro, E. Beck, M. Vandewalker, R. Sigmund, W. Seibold, P. Moronic-Zentgraf, E. Bateman, 2012, *The New England Journal of Medicine*, 367, p. 1203.

- Ultimately all of the studies showed modest improvement in lung function and number of days between severe exacerbations with the addition of tiotropium.

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