RESEARCH LETTER

Limited generalisability of UPLIFT findings to clinical practice

ABSTRACT

Background The findings of the Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) study may be poorly generalisable to tiotropium use in clinical practice.

Methods An audit of 226 patients admitted to Wellington Hospital with a chronic obstructive pulmonary disease exacerbation determined the proportion of patients prescribed tiotropium on discharge that would have been ineligible for inclusion in the UPLIFT study.

Results Among 100 patients prescribed tiotropium, 38/100; 38% (95% CI 28.5% to 48.3%) would have been ineligible for UPLIFT at the time of the hospital discharge due to recent cardiovascular comorbidity or moderate to severe renal impairment.

Conclusions The UPLIFT findings have limited generalisability to over a third of patients prescribed tiotropium following a hospital admission with a chronic obstructive pulmonary disease exacerbation in New Zealand.

The initial clinical research programme of the inhaled anticholinergic agents ipratropium bromide and tiotropium in chronic obstructive pulmonary disease (COPD) suggested their use may increase the risk of serious cardiovascular events and mortality. These concerns were allayed with publication of the large, postregistration study Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) which reported no increased risk of mortality or myocardial infarction with tiotropium HandiHaler. However, the UPLIFT findings may be poorly generalisable to patients with COPD, due to the exclusion of potential research participants with recent cardiac comorbidity or renal impairment.

To determine the generalisability of the UPLIFT findings, we undertook an audit of patients admitted to hospital with an exacerbation of COPD. Discharge coding was used to search for all non-elective admissions to Wellington Hospital with a primary diagnostic code of COPD (International Classification of Diseases, 10th Revision code J44.x). Admissions were examined in chronological order from 1 January 2011 until 100 patients prescribed tiotropium on discharge were included. If a patient had multiple admissions, the first admission with COPD was examined. In New Zealand tiotropium is only available in the HandiHaler 18 μg per actuation preparation.

Data were collected from electronic records, including: tiotropium prescribing, cardiovascular comorbidities, renal function and medications. Comorbidities were further categorised by the cardiovascular and renal exclusion criteria used in postregistration tiotropium HandiHaler studies including the UPLIFT trial:

- cardiac arrhythmias that were deemed unstable or life-threatening, or required intervention or change in drug therapy within the last year
- myocardial infarction that occurred within the last 6 months
- heart failure (New York Heart Association Class III or IV) that required hospital inpatient management within the last year
- moderate to severe renal impairment, which for the audit was defined as a discharge estimated glomerular filtration rate <60 ml/min/1.73 m²

Table 1 Cardiovascular and renal comorbidity and medications prescribed in patients with COPD, according to prescription of tiotropium on discharge

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Tiotropium N (% of 100)</th>
<th>Not on tiotropium N (% of 126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable arrhythmias in the last 1 year</td>
<td>14 (14)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Myocardial infarction in the last 6 months</td>
<td>2 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Heart failure requiring admission in the last 1 year</td>
<td>11 (11)</td>
<td>16 (13)</td>
</tr>
<tr>
<td>Moderate to severe renal impairment on discharge</td>
<td>28 (28)</td>
<td>50* (40)</td>
</tr>
<tr>
<td>Patients with at least one UPLIFT exclusion criterion</td>
<td>38 (38)</td>
<td>49 (39)</td>
</tr>
<tr>
<td>Concurrent medications (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhaled short acting antimuscarinic</td>
<td>14 (14)</td>
<td>71 (56)</td>
</tr>
<tr>
<td>Inhaled LABA</td>
<td>80 (80)</td>
<td>63 (50)</td>
</tr>
<tr>
<td>ICS</td>
<td>88 (88)</td>
<td>89 (71)</td>
</tr>
<tr>
<td>Combined LABA/ICS</td>
<td>61 (61)</td>
<td>40 (32)</td>
</tr>
<tr>
<td>β blocker</td>
<td>6 (6)</td>
<td>11 (9)</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>38 (38)</td>
<td>56 (44)</td>
</tr>
<tr>
<td>ACE-II/Angiotensin II receptor blocker</td>
<td>24 (24)</td>
<td>36 (29)</td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>40 (40)</td>
<td>32 (25)</td>
</tr>
<tr>
<td>Statin</td>
<td>14 (14)</td>
<td>38 (30)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>5 (5)</td>
<td>13 (10)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>13 (13)</td>
<td>19 (15)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>1 (1)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Nitrate</td>
<td>8 (8)</td>
<td>9 (7)</td>
</tr>
</tbody>
</table>

*Total number=124 as two patients in the non-tiotropium group had no renal function measured during admission. COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long acting β agonist; UPLIFT, Understanding Potential Long-term Impacts on Function with Tiotropium.
reflecting the common occurrence of cardiovascular and renal comorbidities in patients admitted with an exacerbation of COPD, and suggesting their presence did not influence its prescription.

In summary, 38% of patients prescribed tiotropium would not have been eligible for inclusion in the UPLIFT study at the time of hospital discharge due to recent cardiovascular or renal comorbidity. The tiotropium HandiHaler datasheet does not give details of the limited evidence-base for tiotropium HandiHaler in patients with COPD with these comorbidities and this is likely to underlie the observed prescription patterns.

We conclude that the UPLIFT findings have limited generalisability to over a third of patients prescribed tiotropium following a hospital admission with a COPD exacerbation in New Zealand.

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**Contributors** SW and JF undertook the data collection which was analysed by MW. All authors contributed to the drafting of the manuscript.

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**Competing interests** RB has been a member of the GlaxoSmithKline (NZ) advisory board, consulted for Cytos Biotechnology and Pharmaxis, received research grants from AstraZeneca, Cephalon, Chiesi, Genentech, GlaxoSmithKline and Novartis, and payment for lectures or support to attend meetings from Boehringer Ingelheim, GlaxoSmithKline, Novartis, Nycomed and Otsuka Pharmaceuticals. JF has received payment for lectures or support to attend meetings from AstraZeneca, Boehringer Ingelheim and Novartis. SW and MW have no competing interests to declare.

**Ethics approval** Ethical approval was obtained from the Central Regional Ethics Committee [12/CEN/16].

**REFERENCES**

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