The case for anti-cholinergics (Dr BJ Lipworth MD)

**Objectives**

- To understand the pharmacology of acetylcholine and muscarinic antagonists in asthma
- To appreciate the potential role of acetylcholine in airway remodeling in asthma
- To know about the key clinical trials involving adding LAMA to ICS or ICS/LABA and relate this to minimal important differences
- To understand the mechanisms for putative synergy between LAMA and LABA
- To consider which patient phenotypes might benefit by using LAMA at step 3/4 of asthma guidelines

**Pharmacology of putative LAMA-LABA synergy**

- Chronic LABA results in pre-junctional beta-2 ADR down regulation and uncoupling - which in turn removes the brake to ACH release – ie LAMA might prevent increased cholinergic transmission due to LABA
- ACH acts via M3 receptors to promote post-junctional beta-2 ADR uncoupling via protein kinase C phosphorylation - ie LAMA might also prevent against heterologous beta-2 ADR desensitisation

**The way forwards**

- Further clinical studies in asthmatic patients are required to look at effects of LAMA on AHR and airway remodeling
- The putative synergy between LAMA and LABA warrants further investigation to assess beta-2ADR desensitization
- Studies to evaluate ICS sparing activity conferred by LAMA during controlled ICS tapering
- Evaluation of role of LAMA in asthmatics who smoke –due ICS resistance

**Key clinical trials in asthma with TIO as add on to ICS or ICS/LABA**

<table>
<thead>
<tr>
<th>Design</th>
<th>Comparison</th>
<th>FEV1</th>
<th>Reversibility</th>
<th>To FEV1</th>
<th>MDR = 0.23 L</th>
<th>MDR = 0.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fardon 2007 XD; Axol</td>
<td>ICS/LABA/TIO18 (vs ICSx2)</td>
<td>51%</td>
<td>23%</td>
<td>0.17L</td>
<td>0.30</td>
<td>0.30</td>
</tr>
<tr>
<td>Peters 2010 XD; 14 wk</td>
<td>ICS/TIO8 (vs ICSx2)</td>
<td>71%</td>
<td>35%</td>
<td>0.10L</td>
<td>0.10</td>
<td>0.23</td>
</tr>
<tr>
<td>Bateman 2011 PG; 16 wk</td>
<td>ICS/TIO5 (vs ICS)</td>
<td>68%</td>
<td>26%</td>
<td>0.15L</td>
<td>0.37L</td>
<td>0.24</td>
</tr>
<tr>
<td>Kerstjens 2014 XD; 8 wk</td>
<td>ICS/LABA/TIO10 (vs ICS/LABA)</td>
<td>51%</td>
<td>14%</td>
<td>0.14L</td>
<td>0.17L</td>
<td>0.10</td>
</tr>
<tr>
<td>Kerstjens 2012 XD; 8 wk</td>
<td>ICS/LABA/TIO5 (vs ICS/LABA)</td>
<td>59%</td>
<td>15%</td>
<td>0.12L</td>
<td>0.11</td>
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</tr>
</tbody>
</table>

Lipworth BJCP 2013;77:55-62

**Which patients to consider LAMA for persistent asthma**

- Refractory to ICS/LABA – as add on – OR instead of LABA
- Freq albuterol use -or albuterol not working as usual (ie x-tolerance)
- Smoking asthmatics
- FEV1< 60% with airway remodeling
- Arg-16 genotype (15%) –ie instead of LABA
- Those requiring beta-blockers

**References**

1. Short et al Heart 2014;100:219-23
10. Short et al AJRCCM; 187 :1308-1314
11. Lipworth BJCP 2013;77:55-62