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Title: Ciclesonide and tiotropium synergistically inhibit airway eosinophilia in a guinea pig model of chronic asthma

Sophie 6621 Bos i.s.t.bos@rug.nl^{1,2}, Herman 6622 Meurs h.meurs@rug.nl^{1,2}, Harm 6623 Maarsingh h.maarsingh@rug.nl^{1,2}, Marieke 6624 Smit marieke.smit@rug.nl^{1,2}, Annet 6625 Zuidhof a.b.zuidhof@rug.nl^{1,2} and Reinoud 6626 Gosens r.gosens@rug.nl^{1,2}. ¹ Molecular Pharmacology, University of Groningen, Groningen, Netherlands and ² GRIAC Research Institute, University of Groningen, Groningen, Netherlands .

Body: Rationale: Using tiotropium, we previously established that acetylcholine regulates allergen-induced airway inflammation and remodelling in guinea pigs. The effect of the combination of a glucocorticosteroid with tiotropium on these processes is currently unknown. Methods: We investigated the effects of tiotropium, alone and in combination with ciclesonide on airway inflammation and remodelling in guinea pigs. Animals were sensitized to ovalbumin and challenged with ovalbumin once (acute model) or once per week for twelve weeks (chronic model). Results: Ovalbumin challenge induced eosinophilia in the acute model. Surprisingly, tiotropium (0.01 – 0.3 mM; nebulizer concentrations) had no effect on airway inflammation in the acute model, whereas ciclesonide (instilled dose range 0.001-1 mg/kg) only had a small anti-inflammatory effect. The combination of tiotropium with ciclesonide showed no anti-inflammatory activity. In striking contrast, both tiotropium and ciclesonide had profound dose-dependent anti-inflammatory effects in the chronic model. Further, both tiotropium and ciclesonide dose-dependently inhibited airway smooth muscle thickening in the chronic model. Importantly, whereas a low dose of tiotropium (0.01 mM) and a low dose of ciclesonide (0.01 mg/kg) each had minimal effects on airway inflammation, they had highly synergistic effects on airway eosinophilia when administered in combination. Conclusion: Tiotropium and ciclesonide inhibit chronic, but not acute, allergen-induced inflammation and airway remodelling. The combination of these drugs produces synergistic anti-inflammatory effects in the chronic model.