Next generation of anti-inflammatory therapy for COPD?

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The MAPK inhibitor RV568 might be the next generation of anti-inflammatory therapy for COPD
<http://ow.ly/vccD30fNP3c>

Cite this article as: Watz H. Next generation of anti-inflammatory therapy for COPD? *Eur Respir J* 2017; 50: 1702084 [https://doi.org/10.1183/13993003.02084-2017].

Symptomatic treatment of chronic obstructive pulmonary disease (COPD) by next-generation bronchodilators has improved considerably over the past decade: Long-acting beta-agonists and long-acting muscarinic antagonists (also as combined fixed-dose inhalation) are now available for long-term maintenance. However, there has been very little progress in developing anti-inflammatory drugs that specifically target inflammation in COPD [1]. More than 10 years ago, several inflammatory pathways and potential drugs in early-phase development for COPD were summarised in two well-known review articles [2, 3]. However, of the drug candidates listed there, only the oral phosphodiesterase-4 inhibitor roflumilast made it to regulatory approval; its anti-inflammatory effects resulted in a reduction of exacerbations and modest improvements in lung function [1, 4]. Other drugs either failed to show a clear benefit, or drug development was stopped because of safety concerns [5]. This has made the past decade disappointing for the development of novel anti-inflammatory therapies in COPD [1].

For a long time, p38 MAPK inhibitors were considered to be ideal drug candidates for an efficacious anti-inflammatory approach in COPD. 1) Macrophages are the orchestrators of chronic pulmonary inflammation in COPD and, with other inflammatory cell types, upregulate the p38 MAPK pathway [6]. 2) p38 MAPK seems to have a role in other chronic inflammatory conditions, such as cardiovascular disease, that affect morbidity and mortality in COPD [7]. p38 MAPK inhibition is thus a holistic therapeutic approach for the inflamed pulmonary and extrapulmonary compartment in COPD. 3) While earlier p38 MAPK inhibitors caused liver toxicity, the second generation showed long-term safety when administered over a period of 6 months, as demonstrated by the p38 MAPK inhibitor losmapimod [8]. However, compared to the convincing body of theoretical evidence for a presumably ideal therapeutic approach, very few data from clinical studies of MAPK inhibition in COPD are available. Thus, the progress in drug development has been slower than anticipated. The largest study (600 patients) with the longest treatment duration (6 months), in which the oral p38 MAPK inhibitor losmapimod was administered along with existing inhaled COPD therapy, suggested that a modest reduction in systemic inflammation and mild lung function benefits (if any) might be expected. However, the effects were not sustainable after 3 months and did not translate into significant changes in exercise tolerance or a clear reduction of exacerbations [8]. So it seems that there are still “many miles to go” for anti-inflammatory treatment, as recently pointed out by CALVERLEY [9], especially for MAPK inhibitors.

Received: Oct 10 2017 | Accepted: Oct 10 2017

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In the current issue of the *European Respiratory Journal*, CHARRON *et al.* [10] present an interesting bench-to-bedside study that evaluates the anti-inflammatory properties of a novel narrow spectrum kinase inhibitor, RV568, which inhibits not only p38 MAPK- α but also p38 MAPK- γ . RV568 might be superior to other MAPK inhibitors evaluated so far. In various cell culture experiments and preclinical models relevant to COPD, the authors convincingly show that this kinase inhibitor produces strong anti-inflammatory activity. However, while the preclinical data are encouraging, we want to know about the clinical data. In a highly selected population of 30 patients with moderate COPD, CHARRON *et al.* [10] demonstrated that inhaled RV568, in addition to existing COPD therapy, can achieve improvements in lung function. This result gives rise to the hope that anti-inflammatory activity will translate into clinically more meaningful outcomes, such as reduction of exacerbations in patients with more advanced disease who are in need of additional therapy. Indeed, a long-term study with 200 patients and 12 weeks of treatment using RV568 will be reported soon (NCT01867762). Because we are still looking for a “COPD-specific statin” with a broad spectrum of anti-inflammatory activity, we eagerly await further study results for RV568.

Acknowledgements

The author thanks Mary McKenney for careful review of the manuscript.

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