that statin treatment did not decrease the risk for pneumonia; rather, if anything, there was a slight increase in pneumonia risk among statin users.

It is pertinent to recognize that observational studies reviewing this subject suffer from methodologic limitations and selection bias. Although metaanalyses of the existing data may shed some light on this issue, we believe it is time for well-designed, randomized controlled clinical trials of statin users with pneumonia. Forward-looking randomized studies are critical because adjustment for comorbidities using purely retrospective data sources (databases, medical records, surveys, or administrative records) lacks the clinical dimensions (eg, functional status, socioeconomic status, comorbidities, and physiologic data) necessary for confidence in study findings. It is important that such trials be powered (n ≥ 1,000) to adequately assess the impact of statins on pneumonia.4,5 Likewise, such studies should also measure and report important clinical outcomes, such as death and complications, at early and late intervals.

Based on the numerous theories and ongoing controversies that surround the effect of statins on pneumonia, it is our hope that randomized controlled trials will be undertaken in the near future to clarify the role of statins in acute illnesses. Without such convincing data, the effect of statins on pneumonia is likely to remain a subject of ongoing debate.

Vineet Chopra, MD
Scott A. Flanders, MD
Ann Arbor, MI

Affiliations: From the Department of Internal Medicine, Division of General Internal Medicine, University of Michigan Health System.

Financial/nonfinancial disclosures: The authors have reported to CHEST that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Correspondence to: Vineet Chopra, MD, 3119 Taubman Health Center, 1500 E Medical Center Dr, SFC 5376, Ann Arbor, MI 48104; e-mail: vineetc@med.umich.edu

© 2010 American College of Chest Physicians. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (www.chestpubs.org/site/misc/reprints.xhtml).

DOI: 10.1378/chest.09-2980

REFERENCES


Possible Role of Statins in COPD-Related Pulmonary Hypertension

To the Editor:

We read with interest the recent article by Chaouat et al (September 2009)1 proposing that interleukin-6 (IL-6), through inflammatory effects, might contribute to pulmonary hypertension in patients with COPD. The role of IL-6 in pulmonary inflammation and matrix remodeling underlying COPD is well recognized.2 The findings of Chaouat et al3 further implicate IL-6 and inflammation in pulmonary hypertension, a well recognized complication of COPD. That pulmonary hypertension affects those with mild-to-moderate COPD suggests that hypoxia, secondary to poor lung function, is not the underlying cause. A similar observation is seen with poor exercise tolerance in COPD, wherein inflammation (eg, IL-6) and oxidant load, not lung function, have been directly implicated in skeletal muscle dysfunction (Fig 1).3 The findings of Chaouat et al3 are made more compelling by the close relationship between serum IL-6 level and pulmonary artery pressure (PAP). In addition, they report a relationship between functional IL-6 genotypes and PAP, which might explain why only some patients with COPD develop pulmonary hypertension.

The link between PAP and inflammation raises a possible therapeutic role for the use of statins that, through inhibition of guanosine triphosphatases (GTPases), lowers serum cytokines such as IL-6.2 It is noteworthy that studies have recently shown that statins lower PAP in humans.4,5 This represents yet another potential benefit of statins in patients with COPD, along with reported reduction in all-cause mortality, mortality from respiratory infection, reduced lung function decline, and lower prevalence of lung cancer.2 The mechanism whereby statins lower PAP is largely unknown but could be mediated through IL-6 inhibition and pulmonary vascular remodeling as suggested by Chaouat et al3 or through inhibition of endothelin-1 by Lee et al.4 In the latter study, the reduction in PAP and endothelin level was associated with an improvement in exercise tolerance of 50%. In a study by the same group, patients with COPD who were randomized to statin therapy experienced a 50% improvement in exercise tolerance that correlated with reduction in serum IL-6.5 Given that IL-6 is known to reduce skeletal muscle function,6 the benefit in exercise tolerance from statins may be through direct effects on skeletal muscle contractility and function.2 Alternatively, through GTPase inhibition, statins might also reduce PAP by abolishing hypoxic pulmonary vasoconstriction.4 Regardless of the mechanism, the study by Chaouat et al3 lends support to the current evidence that systemic antiinflammatory activity (particularly IL-6 inhibition) appears to be an important therapeutic target in patients with COPD.

![Diagram](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/22084/ on 06/25/2017)
We thank Young and Hopkins for their interesting comments on our article (September 2009). They suggest that low-grade systemic inflammation mediated by interleukin-6 (IL-6) may act concomitantly on the skeletal muscles and pulmonary vasculature to impair exercise capacity in patients with COPD. It has been shown that IL-6 is increased in the plasma of patients with COPD and induces the release of acute-phase proteins; furthermore, IL-6 probably has other systemic effects that have not yet been fully elucidated. The hypothesis put forward by Young and Hopkins is partly supported by our results. Our study did not establish a link between systemic inflammation and exercise capacity, because it focused on the mechanism of pulmonary hypertension in patients with COPD. However, we found a weak but significant correlation between the 6-min walk distance and plasma IL-6 level ($r = -0.329$, $P = .04$). However, as stated in our article, the 6-min walk distance did not correlate with mean pulmonary artery pressure. Only very few studies found that mean pulmonary artery pressure determined the severity of exercise limitation in COPD. We fully agree with Young and Hopkins that any drugs designed to improve exercise capacity in COPD must have several targets, as shown in their Figure 1. Indeed, in our opinion, a drug that only lowers mean pulmonary artery pressure may not improve exercise capacity and is probably not worth pursuing. It is also important to emphasize that smoke exposure in genetically susceptible individuals promotes the development of COPD and may also promote the development of comorbidities through systemic inflammation.

Regarding pulmonary hypertension complicating COPD, we already know that the Rho/Rho-kinase pathway, a target of statins, has an important role in pulmonary artery endothelial dysfunction and remodeling. Therefore, current knowledge suggests that statin therapy in patients with COPD may improve the pulmonary hypertension and skeletal muscle dysfunction and may, therefore, increase exercise capacity. To confirm these hypotheses, further pathophysiologic studies of the relationships linking low-grade systemic inflammation to comorbidities in COPD are needed. Finally, large randomized controlled studies investigating the effects and safety of statins in COPD are mandatory to determine whether these drugs should be routinely added to the current long-term pharmacologic regimens.

Ari Chaouat, MD
Vandoeuvre-lès-Nancy, France
Laurent Savale, MD
Serge Adnot, MD
Créteil, France

REFERENCES


Response

To the Editor:

We thank Young and Hopkins for their interesting comments on our article (September 2009). They suggest that low-grade systemic inflammation mediated by interleukin-6 (IL-6) may act concomitantly on the skeletal muscles and pulmonary vasculature to impair exercise capacity in patients with COPD. It has been shown that IL-6 is increased in the plasma of patients with COPD and induces the release of acute-phase proteins; furthermore, IL-6 probably has other systemic effects that have not yet been fully elucidated. The hypothesis put forward by Young and Hopkins is partly supported by our results. Our study did not establish a link between systemic inflammation and exercise capacity, because it focused on the mechanism of pulmonary hypertension in patients with COPD. However, we found a weak but significant correlation between the 6-min walk distance and plasma IL-6 level ($r = -0.329$, $P = .04$). However, as stated in our article, the 6-min walk distance did not correlate with mean pulmonary artery pressure. Only very few studies found that mean pulmonary artery pressure determined the severity of exercise limitation in COPD. We fully agree with Young and Hopkins that any drugs designed to improve exercise capacity in COPD must have several targets, as shown in their Figure 1. Indeed, in our opinion, a drug that only lowers mean pulmonary artery pressure is likely to improve neither the dyspnea nor the exercise capacity and is probably not worth pursuing. It is also important to emphasize that smoke exposure in genetically susceptible individuals promotes the development of COPD and may also promote the development of comorbidities through systemic inflammation.

Regarding pulmonary hypertension complicating COPD, we already know that the Rho/Rho-kinase pathway, a target of statins, has an important role in pulmonary artery endothelial dysfunction and remodeling. Therefore, current knowledge suggests that statin therapy in patients with COPD may improve the pulmonary hypertension and skeletal muscle dysfunction and may, therefore, increase exercise capacity. To confirm these hypotheses, further pathophysiologic studies of the relationships linking low-grade systemic inflammation to comorbidities in COPD are needed. Finally, large randomized controlled studies investigating the effects and safety of statins in COPD are mandatory to determine whether these drugs should be routinely added to the current long-term pharmacologic regimens.

Ari Chaouat, MD
Vandoeuvre-lès-Nancy, France
Laurent Savale, MD
Serge Adnot, MD
Créteil, France

REFERENCES