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Authors' reply

We appreciate the comments from Drs Thickett and Perkins and welcome the opportunity to further discuss the potential roles of interleukin 1 (IL1) in the pathogenesis and repair of acute lung injury.

Regarding the differences in IL1β levels in bronchoalveolar lavage fluid (BALF) obtained from mice and humans, we do not believe that the differences are surprising. IL1β levels are influenced by the lavage volume and the specific assays used. The primary finding is that IL1β mRNA expression and protein levels are markedly increased in the lung early in the course of ventilator induced lung injury.

We agree that the potential broader role of IL1 in alveolar repair and lung fibrosis should be considered when designing future studies of IL1 blockade for acute lung injury. Because of space limitations, we could not elaborate on this important issue in our manuscript.[1] Previous clinical studies have reported that the majority of the pro-inflammatory activity in BALF is attributable to IL1.[2] Through both neutrophil recruitment and an effect of epithelial cells, IL1 induces an increase in permeability to protein.[1] IL1β also downregulates epithelial sodium channel (ENaC) expression and impairs vectorial fluid transport.[3] Together, these effects favour pulmonary oedema formation, the hallmark of acute lung injury and ARDS. Although we have found that IL1 impairs alveolar barrier permeability, previous work from our group has demonstrated that IL1 promotes alveolar epithelial cell migration.[4 5] It is conceivable that blocking IL1 signalling could interfere with normal alveolar epithelial cell migration over the basement membrane during the repair phase of acute lung injury. However, one recent study found that mesenchymal stem cells prevented both acute lung injury and fibrosis following bleomycin administration in mice. The effect was attributable to IL1 receptor antagonist expression in the stem cells.[6] Additionally, chronic overexpression of IL1β induces acute lung injury followed by pulmonary fibrosis,[7] although the mechanisms for the acute inflammatory response and later fibrosis may be distinct.[8] Together these data show that IL1 signalling may govern a broad spectrum of inflammatory and repair processes in the injured lung. Differences in the timing of IL1 blockade may have different effects on injury and repair. Our hypothesis is that early blockade of IL1 signalling may limit the quantity of pulmonary oedema by preserving barrier function and sodium transport, while later IL1 blockade may affect epithelial repair and fibrosis. Additional studies of transgenic mice and IL1 receptor antagonist in other models of acute lung injury and fibrosis may shed more light on how the timing of IL1 signalling during lung injury influences the diverse effects of this cytokine.

Previous clinical trials have not directly addressed the question of the efficacy of IL1 receptor antagonist in patients with acute lung injury. Given the lack of effective therapies for this syndrome of acute respiratory failure in critically ill patients, we believe that further investigation of IL1 receptor antagonist is warranted.

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Pre-cessation varenicline treatment vs post-cessation NRT: an uneven playing field

The study by Aubin *et al*[1] published in this issue is significant in that it is the first head-to-head comparison of the two smoking cessation pharmacotherapies: varenicline and nicotine replacement therapy (NRT). The results suggest that varenicline yielded higher rates of smoking abstinence than NRT. However, an important flaw in the design hampers the interpretation of the results. An imbalance resulted from the fact that the varenicline group began treatment 1 week before the target quit date whereas the NRT group began treatment on the quit date. Although the authors justified this decision based on current manufacturer's instructions for using NRT, the asymmetrical design is problematic.

The problem with the imbalanced design stems from the finding that initiating NRT before the quit date approximately doubles the efficacy of NRT compared with beginning treatment on the quit date.[2] It is plausible that a similar enhancement of efficacy results from initiating varenicline before the quit date. Therefore, beginning varenicline but not NRT before the quit date may have created an unfair advantage for varenicline. Although most studies of pre-cessation NRT have used pretreatment for 2 weeks as opposed to 1 week, it is conceivable that even pre-cessation exposure to treatment for 1 week augments success rates.

A likely mechanism for the enhancement in efficacy with pre-cessation treatment is behavioural extinction.[3] Extinction results from a reduction in the rewarding effects of cigarettes when they are smoked concurrently with NRT or with a nicotinic antagonist such as mecamylamine,[4] or with the nicotinic receptor partial agonist varenicline.[5] This decrement in smoking reward may, in turn, reduce dependence levels and facilitate quitting smoking.

Pre-cessation NRT is not approved by the Food and Drugs Administration, but this recommendation may change as more studies replicate the positive results with pre-cessation NRT.[6] Moreover, the main concern expressed regarding smoking concurrently with NRT—nicotine overdose—can be obviated by switching patients to denicotinised cigarettes during pre-cessation treatment with NRT.[4]

A comparison of NRT and varenicline using equal pre-cessation treatment regimens will ultimately prove informative in evaluating these two treatments.

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Competing interests: The author is a named inventor on several nicotine replacement patents.

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