
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.3 IL1β also downregulates epithelial sodium channel (ENaC) expression and impairs ventialar fluid transport.4 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.5,6 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.7 Additionally, chronic overexpression of IL1β induces acute lung injury followed by pulmonary fibrosis,8 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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REFERENCES


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

The study by Aubin et al7 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 asymmetric 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.1 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.1 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,9 or with the nicotinic receptor partial agonist varenicline.10 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.11 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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REFERENCES

Given the fact that there was no significant difference in the abstinence rates at 12 months between the two treatments, it calls into question the cost-effectiveness of varenicline as a pharmacotherapy for smoking cessation. The courses of treatment used in the trial cost £163.50 and £76.51 for varenicline and NRT, respectively.4 Clinicians are under pressure at all times to cut costs and be evidence-based, and this trial seems to show that there is currently no compelling reason to use the newer, more expensive agent in the smoking cessation clinic, apart from its apparent benefit in reducing craving and some other non-specific effects in the early phases of treatment. We think the conclusions of the trial are presented in such a way as to give more emphasis to the efficacy of varenicline compared with NRT. But it seems that what this study really tells us is that there is no significant difference in long-term abstinence when comparing varenicline with NRT in an open-label comparison.

REFERENCE

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We recognise the relevance of showing long-term outcomes of smoking cessation therapies. However, many drug trials use end of treatment measures as primary outcomes.1 2 Given the high attrition rates during the follow-up phase, choosing long-term primary outcomes has a high impact on the numbers of subjects needed. It is noteworthy that the study cited by Hillman et al failed to show any significant difference between the efficacy of a nicotine patch and placebo at 6 and 12 months of follow-up.3 We would like to acknowledge that the Russell standard includes six standard criteria.4 One of these criteria is to use an “intent to treat” approach in which all randomised subjects are included in the analyses (unless they have died or moved to an untraceable address). Using an all-randomised population, our long-term quit

Clinically significant outcomes in smoking cessation

The study by Aubin et al1 published in this issue comparing varenicline with nicotine replacement therapy (NRT). The authors have shown a significant difference in continuous abstinence rates at the end of treatment of 12 (or 11) weeks, favouring varenicline. However, the beneficial effect is not maintained in a significant fashion up to the end of the study period at 52 weeks. In this context, we would question the validity of measuring abstinence at 12 (or 11) weeks as a primary outcome. It is the long-term outcomes of a smoking cessation therapy that should be most clinically relevant, and therefore the most important finding in this trial. Indeed, the Russell standard recommends that, as a bench mark, quit rates should be assessed at 6 and 12 months and biochemically verified at each point.2 Other comparative studies using NRT have also used 6- or 12-month periods to assess the efficacy.2

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