



Treatment of the acute respiratory distress syndrome with Keratinocyte growth factor: another failure to account

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Acute respiratory distress syndrome (ARDS) is a life-threatening clinical syndrome defined as an acute and severe diffuse lung injury of known origin (1). The mortality rate for ARDS is still high, although it has decreased in the last decades (2). Current treatments are only supportive and there is no effective therapy interfering with the molecular basis of ARDS (3,4): in fact, despite extensive research, almost all promising potential therapies have proven unsuccessful in clinical trials. This is also the case of a randomized, double-blind, placebo-controlled phase II trial evaluating the keratinocyte growth factor (KGF) for the treatment of the ARDS (KARE trial), which has been recently published in the *Lancet Respiratory Medicine* (5).

The primary endpoint of the KARE trial was the improvement of oxygenation index (OI) at day 7, a parameter of severity which correlates with mortality in ARDS (6). Secondary endpoints were OI at days 3 and 14, and a change in respiratory system compliance, in PaO₂/FiO₂ ratio and/or in the SOFA score from baseline to days 3, 7 and 14. The KARE trial eventually failed in any primary or secondary endpoint, apart for OI at day 14 which resulted to be lower in the placebo group. The study had not enough power to assess other outcomes, such as duration of ventilation, intensive-care unit (ICU) stay, intensive care unit and in-hospital mortality, 28- and 90-day mortality. Nevertheless, all these measures were significantly higher in the KGF group compared with the placebo group, whereas there were fewer ventilator-free days in the KGF group and the study drug also carried a higher burden of

adverse events. The Authors concluded that KGF might have been harmful with regards to clinical, not scheduled, outcomes.

KGF is an important biological modulator of alveolar epithelial cell phenotype during the re-epithelization phase which normally follows an acute lung injury (7-10): it has been shown to promote ATII cell proliferation both *in vitro* and *in vivo* and to enhance actin cytoskeletal function near the apical junctions, thus partially resolving paracellular permeability and protecting against epithelial cell damage (11). Therefore, the underlined hypothesis of the KARE trial was that KGF could have been able to accelerate epithelial repair in the injured lung, promoting a faster physiological and clinical recovery from ARDS. However, it should be noticed that alveolar repair and regeneration (or remodelling) is a very complex pathophysiological mechanism in which KGF probably doesn't play the role of the conductor (12). For this reason, similarly to what happened with prostacyclin, statins, granulocyte-macrophage colony-stimulating factor (GM-CSF), surfactant and also KGF applied to sepsis in past years, the use of a single mediator of the regenerative cascade as a potential therapeutic agent might not have been sufficient to improve tissue regeneration in ARDS. Instead, recombinant KGF (Palifermin[®]) is approved and effectively used for the treatment of oral mucositis associated with radiotherapy or chemotherapy in patients affected by haematological disorders (13): in the KARE trial, indeed, the dose and duration of treatment was

established according to the licensed and safe ones for oral mucositis. It is clear that the pathobiological and clinical features of ARDS are diverse and different from oral mucositis, but KGF had previously shown encouraging results also in animal and human models of ARDS (14). Unfortunately, though, there are no reliable models of ARDS reflecting the human syndrome with its high degrees of variability in baseline status, concomitant illnesses, rapidity and severity of lung injury and responses to supportive interventions to date. Moreover, several pulmonary and extrapulmonary precipitants such as sepsis, aspiration, pneumonia and transfusions are associated with the development of ARDS (15): even if these conditions share the same clinical manifestation, this only represents the epiphenomenon of very different pathways. For all these reasons, any clinical trial involving a potential drug which targets a single mediator of the ARDS pathogenetic mechanism risks to be at least underpowered to assess heavy outcomes such as duration of ventilation, ICU stay, ICU and in-hospital mortality, 28- and 90-day mortality.

The KARE trial finding of a higher mortality rate after 28 days in the KGF treated group compared to placebo is in contrast to pre-clinical data in experimental models of ARDS, which supported KGF as a potential therapy. As stated by the authors, it is shareable that the lower mortality in the placebo-treated group may have established a survivor bias explaining the failure of KGF to get the primary outcome, OI at day 7. One can also argue that KGF treatment might have been more harmful in some causative factor driving ARDS than others, but the KARE trial failed to identify any. The authors also claimed other possible theoretical explanations for the trial failure: first, KGF receptors might not be expressed on the target alveolar epithelial cells of patients whose epithelium is injured; second, the intravenous administration of KGF might have been less efficient than the intra-tracheal instillation or inhalation used in most preliminary experimental studies; third, a too short interval between doses might have contributed to a pro-inflammatory effect.

Nevertheless, and honestly speaking, even taking into account every possible bias of the KARE trial it would be easy to guess that there will not be another chance for KGF treatment in ARDS.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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