

IL-6 INHIBITORS IN ARDS: time to step back to mechanism

L. Gandini^{1,2,3}, G. Fior^{1,2}, L.E. See Hoe^{1,2,7}, K. Liu^{1,2}, N.G. Obonyo^{1,2,8,9}, J.Y. Suen^{1,2}, G. Li Bassi^{1,2,4,5,6}, J.F. Fraser^{1,2,4,6}

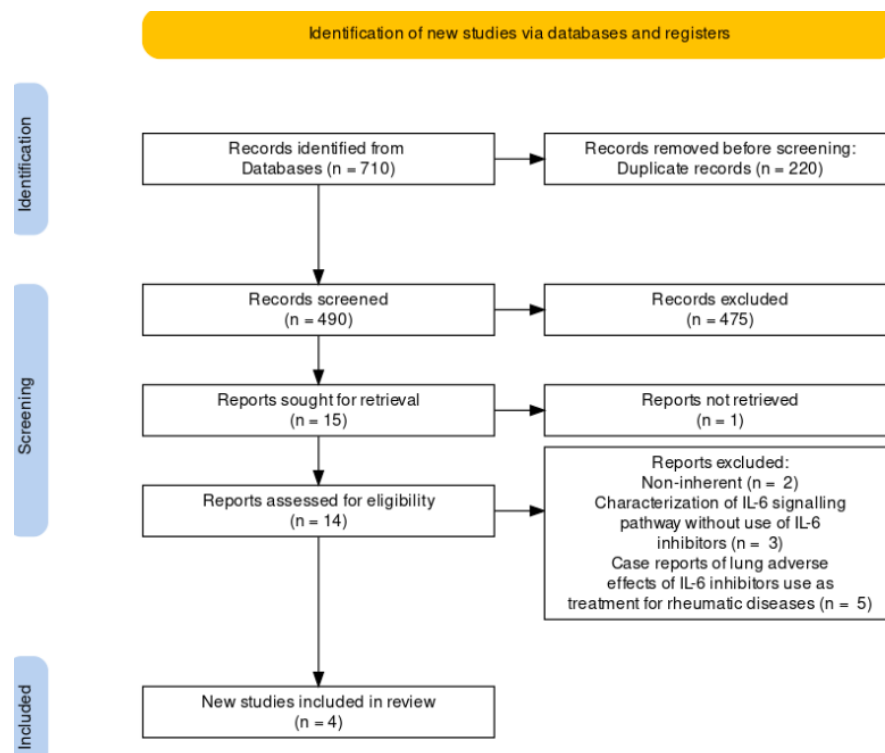
1. Critical Care Research Group, The Prince Charles Hospital, Chermside, Brisbane, QLD, Australia
2. Faculty of Medicine, University of Queensland, Brisbane, QLD, Australia
3. Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy
4. Intensive Care Unit, St Andrews War Memorial Hospital, Brisbane, QLD, Australia
5. Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain
6. Wesley Medical Research, Brisbane, QLD, Australia
7. School of Pharmacy and Medical Sciences, Griffith University, Southport, QLD, Australia
8. Wellcome Trust Centre for Global Health Research, Imperial College London, London, UK
9. KEMRI-Wellcome Trust Research Programme/Initiative to Develop African Research Leaders (IDeAL), Kilifi, Kenya

Background. In 2020, patients with coronavirus disease 2019 (COVID-19) acute respiratory distress syndrome (ARDS) were treated with off-label interleukin-6 (IL-6) inhibitors. However, the role of IL-6 inhibitors for the treatment of ARDS was not yet fully elucidated, and their clinical use was rushed in an attempt to reduce inflammation and improve patient outcomes. Moreover, clinical trials performed during the pandemic have produced conflicting results due to important differences in study designs. Thus, we systematically reviewed the available pre-clinical and clinical evidence to investigate the use of IL-6 inhibitors for ARDS prior to the 2019 pandemic.

Methods. We systematically searched online databases PubMed, EMBASE, CINAHL for all published studies up to 14th March 2022, using a combination of headings and keywords, including three primary sets of terms pertaining to “IL-6 inhibitors” AND “ARDS” NOT “COVID 19”. Titles and abstracts of all identified studies were independently screened by two authors (G.F. and L.G.) and retrieved for duplication checking. After this screening, full-text articles were independently screened for inclusion, and conflicting opinions were resolved by consensus. Reference lists of screened articles were also appraised to identify other possible studies of interest.

Results. A total of 710 studies were identified from the initial search. After the screening, a total of 4 studies were included in the review. Among these, three were preclinical rat studies using models of acute lung injury, and only one clinical paper was identified, presented as case report.

Conclusions. This systematic review highlights the significant lack of evidence in evaluating benefits and safety of IL-6 inhibitors in non-COVID-19 ARDS. Thus, we call attention to the urgent need to conduct high-quality experimental and clinical studies to corroborate the benefits of IL-6 inhibitors (or lack thereof) for treating ARDS, with consideration for inflammatory phenotypic heterogeneity within the general ARDS population.



Flow Diagram 1. Methodological description of systematic review: Interleukin-6 inhibitors treatment in Non-Covid-19 Acute Respiratory Distress Syndrome (adapted from PRISMA Flow Diagram 2020).