studied, which limits generalizability and requires replication in other ancestry groups.

This study provides valuable evidence of a causal link between asthma, GERD, and AD and advances our understanding of the bidirectional relationship of these comorbidities; however, it does not provide insight into functional genetic effects that lead to these relationships. The largest effect sizes were between AD and asthma. On the one hand, this is not surprising given studies showing shared genetic risk between these diseases (13). The atopic march theory, however, supposes that some AD serves as a precursor to asthma (14, 15), and mechanistic studies are needed to determine whether this is the case or whether this relationship reflects simply shared genetic risk. Furthermore, additional studies are needed to better understand the genetic influences on the risk of asthma among those with GERD and vice versa. Assuming this relationship is truly bidirectional, as this MR study and epidemiologic data would suggest, there are likely distinct genetic variants associated with each pathway that may help better understand the mechanisms and genetic factors driving the development of each comorbid condition. ■

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# Galectin-3 Inhibition in COVID-19

Galectins have emerged as molecules that are involved in many immune processes, including neutrophil migration, cytokine release, and the control of T and B cell death (1). Galectin-3, in particular, is highly expressed in monocytes, macrophages, neutrophils, fibroblasts, epithelial cells, and endothelial cells and is secreted in response to inflammatory stimuli (2), potentially amplifying the host inflammatory response during infection (3). It is a marker of severity in acute respiratory distress syndrome (ARDS) not related to coronavirus disease (COVID-19) (4) and has also been recently proposed as a biomarker for COVID-19 severity (5). Galectin-3 stimulates the release of IL-1, IL-6, and tumor necrosis factor alpha (6), which are considered to be important in the pathogenesis of severe COVID-19. A specific galectin-3 inhibitor may have the



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potential to reduce immune-mediated lung injury in COVID-19 more than a drug that targets a single cytokine pathway, such as tocilizumab, which is known to be effective in critically ill patients with COVID-19 (7, 8).

In this issue of the *Journal*, Gaughan and colleagues (pp. 138–149) present results from the DEFINE trial. In this early-phase trial with 41 patients hospitalized with COVID-19, an inhaled galectin-3 inhibitor (GB0139) was investigated (9). It is worth considering that an inhaled formulation of GB0139, as studied here, has the potential for increased delivery to the lung with a reduction in off-target systemic effects. Galecto Biotech, the developer of GB0139, participated in the design and conduct of the study.

GB0139 was found to be safe and well tolerated. Of 20 patients in the GB0139 arm, 14/20 (70%) experienced at least one adverse event as compared with 12/21 (57.1%) in the standard care group. Five mild adverse events in the GB0139 group were considered related to study treatment. Serum galectin-3 decreased over time in the GB0139 group, and inhaled drug was persistently detectable in blood samples.

These results are supported by extensive measurements of biomarker trajectories and cytometric analyses that suggest that GB0139 may modulate biological mechanisms implicated in the host response in COVID-19. It is important to note that the severity of illness as defined by the mean National Early Warning Score 2 (NEWS2) in this cohort was relatively low, and no patients ultimately required admission to the ICU. Current understanding of COVID-19 pathogenesis theorizes an initial viral phase followed by an immune-mediated phase that results in severe illness and ARDS in a subset of patients (10). It would be interesting to speculate that GB0139 might be most useful in limiting excessive host inflammatory response associated with severe disease. However, unfortunately, this subset of patients was not studied in this trial. It would have been interesting to see the cytokine trajectory in patients who become severely unwell and how that might be attenuated by GB0139.

The attenuation in the rise of D-dimer in the GB0139 group, as well as the decrease in the fibrinogen-to-plasminogen ratio and the increase in platelet count, is interesting to note. D-dimers in the range of 69,000 ng/ml were recorded in the standard care group, with the highest recorded value in the GB0139 group being less than one tenth that value. Elevated D-dimer is a marker of poor outcome in COVID-19, and it is well recognized that thrombosis may play a significant part in its pathogenesis (11). The study also included measurement of plasminogen activator inhibitor-1, which was found to decrease in both trial arms but remained lower in the group treated with GB0139. Plasminogen activator inhibitor-1 is a potent positive regulator of inflammation and thrombosis. On the basis of these results, it is possible to hypothesize that GB0139 could provide benefit through the prevention of severe thrombotic complications.

Gaughan and colleagues also demonstrated a faster rate of decrease of YKL-40 in the GB0139 group, supported by flow cytometry demonstrating monocyte transformation from a profibrotic to an antifibrotic phenotype. YKL-40 is associated with pulmonary fibrosis and may be a marker of poor prognosis in COVID-19 (12). Most evidence for the role of YKL-40 comes from studies in idiopathic pulmonary fibrosis. However, higher levels of YKL-40 have been reported in COVID-19 compared with an idiopathic pulmonary fibrosis control population, as well as being associated with increasing risk of ICU admission and multiorgan failure (12).

Despite the promising biomarker findings, the GB0139 arm had fewer oxygen-free days than the standard care group (19/123 [15%] vs. 29/86 [34%]; rate ratio, 0.45; 95% credible interval, 0.25–0.82). This raises the possibility that the biomarkers measured may not be valid surrogate measures for clinical outcomes, although it must be reiterated that this trial was not adequately powered to detect differences in clinical outcomes. Indeed, the difference in oxygen-free days could be due to the imbalance in baseline characteristics in the GB0139 and the standard of care arm, with significantly more patients in the GB0139 arm having a higher baseline NEWS2 score.

Taken together, the biomarker data in the DEFINE trial suggest that GB0139 may attenuate inflammation, coagulopathy, and fibrosis in COVID-19. However, this is a small study population, and results should be interpreted cautiously. In addition, some results were observed only in the subset of patients with a NEWS2 score $\geq 4$, which may further increase the risk of bias due to the smaller sample size and amplified effect of outliers.

The authors are to be commended for successfully completing a rigorous early-phase study in the setting of the COVID-19 pandemic. The data presented support the need for a larger trial. Although the data are encouraging and hypothesis-generating, we will have to wait for larger studies of GB0139 to determine the role of galectin-3 inhibition in COVID-19. With the declining incidence of COVID-19, investigating galectin-3 inhibition in ARDS from other causes is also likely to be an additional important research priority. ■

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# COVID-19 Extracorporeal Membrane Oxygenation Outcomes: Reporting One-Year Multidimensional Outcomes as Standard Practice

One- and two-year outcomes after coronavirus disease 2019 (COVID-19) critical illness have been published by several international groups to date (1–5). The post–COVID-19 condition for critical illness survivors recapitulates the robust multimorbidities observed in severely ill patients after acute respiratory distress syndrome (ARDS) reported over the past several decades (6, 7). With the accrual of large numbers of post–COVID-19 critical illness survivors, it is imperative to report the spectrum of morbidity, especially for those most severely affected and requiring extracorporeal membrane oxygenation (ECMO). Granular one-year follow-up on COVID-19 ECMO survivors informs durable multimorbidities, care transitions, healthcare use, and cost. It also advances the dialogue about resource allocation, informed consent about the initiation and continuation of ECMO, and accountability for patients, caregivers, and healthcare systems.

In this issue of the *Journal*, Chommeloux and colleagues (pp. 150–159) contribute important data on one-year multidimensional outcomes among individuals with COVID-19–related ARDS treated with ECMO (8). These prospective data from multiple centers across France, with close to 80% follow-up, have laudable generalizability and internal validity. COVID-19 ECMO survivors were young (mean age, 47 yr) and had few comorbidities, and most were working full-time before COVID-19. Similar to the literature on non–COVID-19 ARDS outcomes, there was recovery of normal to near normal pulmonary function by 6 months, with an isolated decrement in diffusion capacity persisting to 12 months. Pulmonary outcomes were discordant with reported physical disability, as noted previously in ARDS survivors and attributed to myriad extrapulmonary physical morbidities (6, 7). Anxiety and depressive symptoms were prevalent (42–44%), and post-traumatic stress disorder (PTSD) (42%) was higher at one year compared with individuals with non–COVID-19 ARDS on ECMO at a similar time point (9). Only 38% of patients had returned to work at one year.

This is the largest comprehensive evaluation of one-year outcomes after extracorporeal life support (ECLS) for COVID-19. Notable strengths of this unique study include a multicenter sample, serial collection of granular multidimensional and patient-important outcomes, completeness of follow-up, and in-person evaluation when feasible. The authors comment on nerve injury related to proning and ECMO and the impact of poor cosmesis, illustrated with powerful images in their paper. Sexual dysfunction was evaluated, and only 31% of patients reported return to baseline sexual function at one year. These patient- and family-important outcomes are seldom included in follow-up but should be routinely prioritized. There is scant literature on post-ICU sexual dysfunction, but an earlier study by



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