Irish Journal of Medical Science (1971 -) (2023) 192:831–832
https://doi.org/10.1007/s11845-022-03068-w

LETTER TO THE EDITOR

Emergency myelopoiesis in critical illness: lessons from the COVID-19 pandemic

David N. O'Driscoll[1]

Received: 5 June 2022 / Accepted: 11 June 2022 / Published online: 16 June 2022

Keywords COVID-19 · Emergency myelopoiesis · Immunomodulation · Sepsis

To the Editor:

The first cases of SARS-CoV-2 viral infection and subsequent outbreaks were described in November 2019 in Wuhan, China. Since then, the global COVID-19 pandemic has ensued, with up to 5% of patients developing acute respiratory distress syndrome (ARDS) in some reports, often necessitating mechanical ventilation [1]. The clinical course of COVID-19 is remarkably heterogeneous, despite the identification of risk factors including male sex, chronic airway disease, obesity, cardiovascular disease, type 2 diabetes, and immunosuppression, amongst others. This heterogeneity may be due to biological differences in the host response to SARS-CoV-2. Immunomodulatory therapies have been investigated in parallel to specific antivirals targeting SARS-CoV-2 and its variants. For example, the ACTT-2 trial investigating baricitinib (small-molecule inhibitor of JAK1/JAK2 which arrests downstream immune signalling) in combination with remdesivir described 30% higher odds of improvement in clinical status at day 15 in hospitalised adults with COVID-19 [2]. Similarly, tocilizumab (anti-interleukin-6 receptor monoclonal antibody) [3], dexamethasone [4], and convalescent plasma [5] have shown outcome benefits through host immunomodulation. Despite this, robust evidence for the efficacy of many such interventions remains unclear, and the beneficial effects likely rely on treating the right patient cohorts at the right time in their illness [6].

The complex pathophysiology of COVID-19 is distinct from other viral pneumonitides and variance exists between individuals. The first phase appears to begin with cytotoxic epithelial injury as viral replication stimulates monocyte, neutrophil, and T-cell trafficking to respiratory tissue [7]. The mechanisms of a second phase, characterised by endothelial insult with ensuing inflammation (mediated by cytokines, reactive oxygen species, neutrophil dysfunction, and acute-phase reactants) with subsequent coagulopathy, are less well understood [8]. Immunophenotyping in COVID-19 has been performed by multiple groups, and alterations in myeloid compartments have been associated with severe disease [9], alluding to the integral role of emergency myelopoiesis COVID-19 pathophysiology.

Emergency myelopoiesis is essential to control infection, characterised by inflammation-induced haematopoiesis to replenish immune cells in the periphery. Following the exodus of myeloid cells (predominantly neutrophils and monocytes) in response to both direct and indirect molecular signals, haematopoietic stem cells in the bone marrow and spleen expand to form predominantly forming common myeloid and granulocyte–macrophage progenitor colony-forming units, which later differentiate into more mature myeloid populations [10]. Townsend et al. [11] demonstrated a shift towards emergency myelopoiesis, characterised by immature and pro-inflammatory circulating myeloid cell populations (reduced HLA-DR + monocytes and CD10 + neutrophils), is associated with severe COVID-19 in a prospective study. This phenotype was associated with poor clinical outcomes, with progressive lymphopaenia and anaemia, which is reflected in other studies of sepsis [12] and is identifiable early in the disease course. This phenotype may also reflect relative immunoparesis, a phenomenon associated with increased morbidity and mortality, notably in the anti-inflammatory phase of sepsis and shock.

Additionally, diverse populations of myeloid-derived suppressor cells (MDSCs) expand in emergency myelopoiesis. These cells exhibit diverse modulatory effects, and their persistence has been associated with poor outcomes in sepsis via host immunosuppression [13] and in COVID-19 severity

✉ David N. O'Driscoll
odriscd3@tcd.ie

[1] Department of Medicine, Mater Misericordiae University Hospital, Dublin, Ireland

[14]. MDSCs have also been implicated in the development of the post-intensive care syndrome (PICS), typified by persistent immune dysfunction and a reduction in quality of life metrics [15].

Immune dysregulation in critically ill patients is challenging, and novel approaches to risk stratification, biomarker discovery, and assessment of cellular immune function are required. Quantification of emergency myelopoiesis with routine laboratory techniques is feasible and may facilitate temporal measurement of immune function, assisting with prognostication and identification of patients progressing to immunoparesis. Concern over impaired clearance of the causative microorganism and risk of secondary infections with immunomodulatory therapy is justified, therefore identifying at-risk patients and instituting treatment early may provide the most benefit. Emerging data also highlight the recognition of emergency myelopoiesis in other contexts, such as all-cause sepsis and other long-term sequelae.

In summary, emergency myelopoiesis may be interrogated and harnessed for modulation in the critically ill. This has been underscored by recent research on the COVID-19 pandemic which may translate to beneficial clinical endpoints. Further international, multi-centre research across various disease states and populations will help delineate this relationship further.

Declarations

Conflict of interest The author declares no competing interests.

References

1. Phua J, Weng L, Ling L et al (2020) Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations. Lancet Respir Med 8(5):506–517
2. Kalil A, Patterson T, Mehta A et al (2021) Baricitinib plus remdesivir for hospitalized adults with COVID-19. N Engl J Med 384(9):795–807
3. Salama C, Han J, Yau L et al (2021) Tocilizumab in patients hospitalized with COVID-19 pneumonia. N Engl J Med 384(1):20–30
4. RECOVERY Collaborative Group (2021) Dexamethasone in hospitalized patients with COVID-19. New Engl J Med 384(8):693–704
5. Joyner M, Senefeld J, Klassen S et al (2020) Effect of convalescent plasma on mortality among hospitalized patients with COVID-19: initial three-month experience
6. van de Veerdonk FL, Giamarellos-Bourboulis E, Pickkers P et al (2022) A guide to immunotherapy for COVID-19. Nat Med 28:39–50
7. Xu Z, Shi L, Wang Y et al (2020) Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 8(4):420–422
8. Osuchowski M, Winkler M, Skirecki T et al (2021) The COVID-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity. Lancet Respir Med 9(6):622–642
9. Schulte-Schrepping J, Reusch N, Paclik D et al (2020) Severe COVID-19 is marked by a dysregulated myeloid cell compartment. Cell 182(6):1419-1440.e23
10. Cuenca A, Cuenca A, Gentile L et al (2014) Delayed emergency myelopoiesis following polymicrobial sepsis in neonates. Innate Immun 21(4):386–391
11. Townsend L, Dyer A, Naughton A et al (2022) Severe COVID-19 is characterised by inflammation and immature myeloid cells early in disease progression. Heliyon 8(4):e09230
12. Cheron A, Floccard B, Allaouchiche B et al (2010) Lack of recovery in monocyte human leukocyte antigen-DR expression is independently associated with the development of sepsis after major trauma. Crit Care 14(6):R208
13. Uhel F, Azzaoui I, Grégoire M et al (2017) Early expansion of circulating granulocytic myeloid-derived suppressor cells predicts development of nosocomial infections in patients with sepsis. Am J Respir Crit Care Med 196(3):315–327
14. Rowlands M, Segal F, Hartl D (2021) Myeloid-derived suppressor cells as a potential biomarker and therapeutic target in COVID-19. Front Immunol 12
15. Mathias B, Delmas A, Ozrazgat-Baslanti T et al (2017) Human myeloid-derived suppressor cells are associated with chronic immune suppression after severe sepsis/septic shock. Ann Surg 265(4):827–834