



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

strict lockdown; therefore, all contacted patients who freely agreed to participate in the survey gave oral consent, according to the policy of our institutions.

**Clodoveo Ferri, Dilia Giuggioli, Vincenzo Raimondo, Lorenzo Dagna, Valeria Riccieri, Elisabetta Zanatta, Serena Guiducci, Antonio Tavoni, Rosario Foti, Giovanna Cuomo, Rossella De Angelis, Franco Cozzi, Giuseppe Murdaca, Ilaria Cavazzana, Nicoletta Romeo, Veronica Codullo, Francesca Ingegnoli, Roberta Pellegrini, Giuseppe Varcasia, Alessandra Della Rossa, Maria De Santis, Giuseppina Abignano, Michele Colaci, Maurizio Caminiti, Massimo L'Andolina, Ennio Lubrano, Amelia Spinella, Federica Lumetti, Giacomo De Luca, Silvia Bellando-Randone, Elisa Visalli, Silvia Bilia, Daiana Giannini, Francesco Masini, Greta Pellegrino, Erika Pigatto, Elena Generali, Francesca Dall'Ara, Giuseppa Pagano Mariano, Simone Barsotti, Giorgio Pettiti, Giovanni Zanframundo, Raffaele Brittelli, Vincenzo Aiello, Daniela Scorpiniti, Tommaso Ferrari, Rodolfo Caminiti, Corrado Campochiaro, Salvatore D'Angelo, Florenzo Iannone, Marco Matucci-Cerinic, Andrea Doria, Mario Miccoli, Poupak Fallahi, \*Alessandro Antonelli, for the COVID-19 & Autoimmune Systemic Diseases Italian Study Group**  
[alessandro.antonelli@med.unipi.it](mailto:alessandro.antonelli@med.unipi.it)

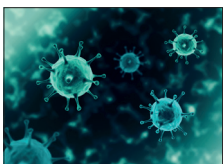
Rheumatology Unit, School of Medicine, University of Modena and Reggio Emilia, Modena, Italy (CF, DGIU, AS, FL); Rheumatology Clinic Madonna dello Scoglio Cotronei, Crotona, Italy (CF, VRa, RB, VA, DS, RC); Ospedale S Raffaele, Milan, Italy (LD, GDL, CC); Department of Rheumatology, Sapienza-University of Rome, Rome, Italy (VRi, GPel); Department of Rheumatology, University of Padova, Padova, Italy (EZ, AD); Department of Rheumatology, University of Florence, Florence, Italy (SG, SB-R, MM-C); Department of Clinical Immunology (AT, SBI, DGia), Department of Rheumatology (ADR, SBA), Department of Clinical and Experimental Medicine (MM, AA), and Department of Translational Research and New Technologies in Medicine and Surgery (PF), University of Pisa, Pisa, Italy; AOU Policlinico Vittorio Emanuele, Catania, Italy (RF, EV); University of Campania Luigi Vanvitelli, Naples, Italy (GC, FM); Rheumatology Clinic, Department of Clinical and Molecular Sciences, Marche Polytechnic University, Ancona, Italy (RDA); Ospedale Villa Salus Mestre, Mestre, Italy (FC, EP); Ospedale Policlinico

S Martino-University of Genova, Genova, Italy (GM); Department of Rheumatology, Spedali Civili di Brescia, Brescia, Italy (IC, FD'A); ASO S Croce e Carle, Cuneo, Italy (NR, GPet); Department of Rheumatology, Policlinico San Matteo, Pavia, Italy (VC, GZ); Department of Rheumatology, University of Milan, Milan, Italy (Fin); Rheumatology Complex Unit, Medicina Interna M Valentini PO Annunziata Cosenza, Cosenza, Italy (RP); Rheumatology Section, Ospedale Castrovillari, Cosenza, Italy (GV, TF); Istituto Clinico Humanitas, Milan, Italy (MDS, EG); Azienda Ospedaliera Regionale, San Carlo di Potenza, Potenza, Italy (GA, SD'A); Department of Rheumatology, University of Catania, Catania, Italy (MCo); Departmental Rheumatology Unit, Grande Ospedale Metropolitano, Reggio Calabria, Italy (MCA, GPM); Rheumatology Outpatient Clinic, Azienda Sanitaria Provinciale, Tropea Hospital, Vibo Valentia, Italy (ML'A); Department of Rheumatology, Università del Molise, Campobasso, Italy (EL); Rheumatology Complex Unit, Dipartimento dell'Emergenza e Traipianti di Organi, Università di Bari, Bari, Italy (Fla)

- 1 WHO. Coronavirus disease 2019 (COVID-19): situation report, 51. March 11, 2020. [https://www.who.int/docs/default-source/coronavirus/situation-reports/20200311-sitrep-51-covid-19.pdf?sfvrsn=1ba62e57\\_10](https://www.who.int/docs/default-source/coronavirus/situation-reports/20200311-sitrep-51-covid-19.pdf?sfvrsn=1ba62e57_10) (accessed March 11, 2020).
- 2 Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020; **382**: 1708–20.
- 3 Gianfrancesco MA, Hyrich KL, Gossec L, et al. Rheumatic disease and COVID-19: initial data from the COVID-19 Global Rheumatology Alliance provider registries. *Lancet Rheumatol* 2020; **2**: e250–53.
- 4 Ferri C, Giuggioli D, Raimondo V, et al. COVID-19 and rheumatic autoimmune systemic diseases: report of a large Italian patients series. *Clin Rheumatol* 2020; **39**: 3195–204.
- 5 Fredi M, Cavazzana I, Moschetti L, Andreoli L, Franceschini F, Brescia Rheumatology COVID-19 Study Group. COVID-19 in patients with rheumatic diseases in northern Italy: a single-centre observational and case-control study. *Lancet Rheumatol* 2020; **2**: e549–56.
- 6 Lu C, Li S, Liu Y. Role of immunosuppressive therapy in rheumatic diseases concurrent with COVID-19. *Ann Rheum Dis* 2020; **79**: 737–39.
- 7 Denton CP, Khanna D. Systemic sclerosis. *Lancet* 2017; **390**: 1685–99.
- 8 Avouac J, Airó P, Carlier N, Matucci-Cerinic M, Allanore Y. Severe COVID-19-associated pneumonia in 3 patients with systemic sclerosis treated with rituximab. *Ann Rheum Dis* 2020; published online June 5. <http://dx.doi.org/10.1136/annrheumdis-2020-217864>.
- 9 Bellan M, Parisi S, Stobbione P, et al. Impact of the Covid-19 outbreak on an Italian cohort of systemic sclerosis patients. *Scand J Rheumatol* 2020; **49**: 505–06.
- 10 Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020; **395**: 1417–18.



## Divergent effects of acute versus chronic glucocorticoids in COVID-19



Published Online  
 January 28, 2021  
[https://doi.org/10.1016/S2665-9913\(21\)00005-9](https://doi.org/10.1016/S2665-9913(21)00005-9)

The COVID-19 pandemic has precipitated a search for both effective treatments and patient factors that predict poor outcome. Although agents ranging from convalescent plasma to Janus kinase (JAK) inhibitors have been trialled, to date the best evidenced acute therapy for severe COVID-19 is glucocorticoids. However, chronic glucocorticoid use has been found to increase the risk of poor outcomes in patients with COVID-19. This situation creates an interesting dichotomy.

Much of the pathology of severe acute COVID-19 is driven by the consequences of unconstrained activity of the host inflammatory response. Glucocorticoids have

been found to be an effective treatment for COVID-19 in the acute setting, with 6 mg of dexamethasone (equivalent to 40 mg daily of prednisone) daily for up to 10 days reducing mortality from 25.7% to 22.9% (rate ratio [RR] 0.83, 95% CI 0.75–0.93).<sup>1</sup> These results were even more striking in patients who required oxygen (RR 0.82, 95% CI 0.72–0.94 ) or invasive ventilation (RR 0.64, 95% CI 0.51–0.81); notably those receiving no respiratory support did not benefit.

In contrast to the effect of acute glucocorticoids, registry data suggests that chronic glucocorticoids increase the odds of hospitalisation for COVID-19 in patients with

rheumatic disease, with an adjusted odds ratio (aOR) of 2.05 (95% CI 1.06–3.96) in those taking 10 mg or more prednisone equivalent.<sup>2</sup> Patients with inflammatory bowel disease on any dose of systemic glucocorticoids had increased odds of COVID-19 related death (OR 11.62, 95% CI 2.09–64.74).<sup>3</sup> In both these studies, logistic regression models adjusted for disease severity to address confounding by indication. This deleterious effect has even been reported for inhaled therapy, wherein patients with chronic obstructive pulmonary disease and asthma using inhaled glucocorticoids had an increased risk for COVID-19 death compared with those taking other respiratory medications (eg, people with chronic obstructive pulmonary disease taking any dose, adjusted hazard ratio [aHR] 1.39, 95% CI 1.10–1.76; people with asthma taking high dose, aHR 1.55, 95% CI 1.10–2.18).<sup>4</sup>

Why might this dichotomy exist? These divergent effects of glucocorticoids exist alongside the divergent effects of the immune system itself on health—profound immunodeficiency is just as harmful as its opposite, the excessive immunity, as exemplified by autoimmune disease but also by systemic inflammatory reactions during acute COVID-19. Glucocorticoids suppress effector T cells but can increase regulatory T-cell numbers,<sup>5</sup> indicating the sophistication of the actions of supraphysiological concentrations of glucocorticoids on immunity. However, the role of endogenous glucocorticoids in controlling immune responses is context-dependent, with acute stress inducing activation of the hypothalamo-pituitary-adrenal (HPA) axis and suppressing glucocorticoid production,<sup>6</sup> but chronic stress, which disrupts the HPA axis differently, able to trigger the onset of autoimmune disease.<sup>7</sup> This situation highlights the additional impact of time, or chronicity, on the net outcome of the interaction between glucocorticoids and immunity. So, are the divergent effects of acute glucocorticoids benefiting established COVID-19 versus chronic steroids increasing the risk of poor outcomes, due to dose, timing, or something else?

The short answer is that we do not yet know. Why should acute glucocorticoids work? Many studies indicate the massive overproduction of multiple cytokines during acute COVID-19, indicative of hyperinflammation. Clinically relevant therapeutic effects in acute COVID-19 of targeted anti-cytokine therapies such as tocilizumab (anti-interleukin-6 receptor) have not been shown;<sup>8</sup> in contrast, glucocorticoids, via their direct actions on the promiscuous transcription factor NF- $\kappa$ B as well as the induction of

anti-inflammatory proteins such as glucocorticoid-induced leucine zipper (GILZ), have extremely broad immune effects. While we await understanding of the chief cytokine culprits of severe COVID-19, it might be that broad targeting is more fruitful; murine studies suggest the potential of greater effects of dual cytokine blockade than those of blocking individual cytokines.<sup>9</sup> This is further supported by the evidence, albeit limited, that JAK kinase inhibitors such as baricitinib, which also have a mechanism encompassing blockade of multiple cytokines, can be beneficial for the treatment of COVID-19.

How does this differ from the effect of chronic glucocorticoids on risk of severe COVID-19? Known risks for poor COVID-19 outcomes include obesity and other adverse health indicators, which might be associated with glucocorticoid use.<sup>10</sup> Intriguingly, suppression of type I interferon (IFN) by neutralising anti-IFN autoantibodies, which in some cases even pre-date SARS-CoV-2 infection, has been shown to correlate strongly with adverse outcomes in COVID-19;<sup>11</sup> type I IFNs are a crucial component of the innate immune response to viral infection. The effects of glucocorticoids on the IFN pathway remain incompletely understood; low pharmacological concentrations of glucocorticoids such as those achieved with oral doses of glucocorticoids do not appear to suppress IFN production, as Toll-like receptor-dependent activation of NF- $\kappa$ B during the events leading to IFN transcription evades glucocorticoid inhibition.<sup>12</sup> However, glucocorticoids do suppress events entrained by IFN receptor ligation, typically measured via readouts of IFN gene expression, including during viral respiratory infection. These effects can result in increased viral replication, another risk factor for poor COVID-19 outcomes.<sup>13</sup> Resting levels of the glucocorticoid mediator GILZ constrain initiation of T-cell and B-cell activation,<sup>14,15</sup> potentially explaining weaker adaptive immune responses during initial stages of infection in patients taking glucocorticoids that could also result in higher viral load.

In the end, countless hypotheses could explain the divergence between beneficial acute and harmful chronic effects of glucocorticoids on COVID-19; resolving this will require intensive biological profiling and potentially machine learning approaches. The data demonstrate that broad suppression of the aberrant hyperinflammatory response during acute severe COVID-19 is beneficial, however this has only been shown during a critical window of illness severity, and this finding is at odds with higher

risk in patients taking chronic, lower dose glucocorticoids. There is little doubt that even with widespread vaccination COVID-19 will remain a threat for a subset of patients, potentially including those receiving glucocorticoid treatment for autoimmune disease. Therefore, it behoves us to continue to investigate and clarify the divergent effects of treatments such as glucocorticoids in order to educate patients and health-care providers.

PR reports personal fees from Abbvie, Eli Lilly, Gilead, and Roche; grants and personal fees from Novartis, Janssen, UCB Pharma, and Pfizer; and non-financial support from BMS, outside the submitted work. EM reports grants and personal fees from Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Janssen, GlaxoSmithKline, and EMD Serono; personal fees from Biogen, AbbVie, Wolf, Neovacs, UCB, Sanofi, Novartis, and Amgen; outside the submitted work.

\*Philip C Robinson, Eric Morand

philip.robinson@uq.edu.au

University of Queensland School of Clinical Medicine, Herston, QLD 4006, Australia (PCR); Centre for Inflammatory Disease, Monash University, Melbourne, VIC, Australia (EM)

- 1 The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 - Preliminary Report. *N Engl J Med* 2020; published online July 17. <https://doi.org/10.1056/NEJMoa2021436>.
- 2 Gianfrancesco M, Hyrich KL, Al-Adely S, et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Ann Rheum Dis* 2020; **79**: 859–66.
- 3 Brenner EJ, Ungaro RC, Gearty RB, et al. Corticosteroids, but not TNF antagonists, are associated with adverse COVID-19 outcomes in patients with inflammatory bowel diseases: results from an international registry. *Gastroenterology* 2020; **159**: 481–491.

- 4 Schultze A, Walker AJ, MacKenna B, et al. Risk of COVID-19-related death among patients with chronic obstructive pulmonary disease or asthma prescribed inhaled corticosteroids: an observational cohort study using the OpenSAFELY platform. *Lancet Respir Med* 2020; **8**: 1106–20.
- 5 Chen X, Oppenheim JJ, Winkler-Pickett RT, Ortaldo JR, Howard OM. Glucocorticoid amplifies IL-2-dependent expansion of functional FoxP3(+) CD4(+)CD25(+) T regulatory cells in vivo and enhances their capacity to suppress EAE. *Eur J Immunol* 2006; **36**: 2139–49.
- 6 Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. *N Engl J Med* 1995; **332**: 1351–62.
- 7 Jones SA, Morand EF. Glucocorticoids in 2015: New answers to old problems. *Nat Rev Rheumatol* 2016; **12**: 73–74.
- 8 Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with Covid-19. *N Engl J Med* 2020; **383**: 2333–44.
- 9 Karki R, Sharma BR, Tuladhar S, et al. Synergism of TNF- $\alpha$  and IFN- $\gamma$  triggers inflammatory cell death, tissue damage, and mortality in SARS-CoV-2 infection and cytokine shock syndromes. *Cell* 2021; **184**: 149–68.
- 10 Laugesen K, Petersen I, Pedersen L, Breinholt Larsen F, Jørgensen JOL, Sørensen HTT. Prevalence of lifestyle characteristics in glucocorticoid users and non-users: a Danish population-based cross-sectional study. *BMJ Open* 2019; **9**: e030780–89.
- 11 Bastard P, Rosen LB, Zhang Q, et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science* 2020; **370**: eabd4585.
- 12 Guiducci C, Gong M, Xu Z, et al. TLR recognition of self nucleic acids hampers glucocorticoid activity in lupus. *Nature* 2010; **465**: 937–41.
- 13 Thomas BJ, Porritt RA, Hertzog PJ, Bardin PG, Tate MD. Glucocorticosteroids enhance replication of respiratory viruses: effect of adjuvant interferon. *Sci Rep* 2014; **4**: 7176.
- 14 Jones SA, Toh AE, Odobasic D, et al. Glucocorticoid-induced leucine zipper (GILZ) inhibits B cell activation in systemic lupus erythematosus. *Ann Rheum Dis* 2016; **75**: 739–47.
- 15 Jones SA, Perera DN, Fan H, Russ BE, Harris J, Morand EF. GILZ regulates Th17 responses and restrains IL-17-mediated skin inflammation. *J Autoimmun* 2015; **61**: 73–80.



## A call for papers: EULAR 2021

Much has changed since the launch of *The Lancet Rheumatology* in 2019; since early 2020, the world has been gripped by the COVID-19 pandemic, a crisis that has seen rheumatology and rheumatologists rise to the forefront of cross-specialty collaborations, clinical trials, and front-line patient care. Despite the challenges of a global pandemic, robust research and trials on rheumatic and musculoskeletal conditions have forged ahead.

To highlight some of the latest research in the field, *The Lancet Rheumatology* is planning to publish late-breaking content to coincide with the Annual European Congress of Rheumatology (EULAR 2021), which will be held virtually on June 2–5, 2021.

We welcome high-quality submissions across all areas of rheumatology and musculoskeletal disease, particularly clinical trials and research that will change clinical practice or current thinking. We are also keen to see submissions that bridge specialities; those in which

traditional rheumatic and musculoskeletal diseases might overlap with and reciprocally inform other conditions, as has been so powerfully demonstrated for COVID-19.

The journal has a rigorous fast-track peer review process for original research, which reflects our belief in the timely dissemination of high-quality data to the community. If you are presenting your research at EULAR 2021, we can time publication to your presentation. Please submit your paper through our online submission system mentioning this call for papers in your covering letter. The deadline for submissions is Friday, March 12, 2021. We look forward to receiving your research submissions and continuing to work alongside you to advance the field of rheumatology and help improve the lives of patients.

Heather Van Epps  
rheumatology@lancet.com

The Lancet Rheumatology, London EC2Y 5AS, UK



Published Online

February 9, 2021

[https://doi.org/10.1016/S2665-9913\(21\)00040-0](https://doi.org/10.1016/S2665-9913(21)00040-0)

For EULAR 2021 see

<https://congress.eular.org/>

To submit a manuscript to

*The Lancet Rheumatology* go to

<https://www.editorialmanager.com/tlrheu/default.aspx>