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EDITORIAL

The "Infodemic" of COVID-19

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Some in the medical publishing world have observed an "infodemic" occurring alongside the coronavirus disease 2019 (COVID-19) pandemic. One might define an infodemic as a contagious disease infecting our information culture. As the Editors of *Arthritis & Rheumatology*, tasked with conducting, reviewing, reporting, and translating science to the rheumatic disease community, we agree with this diagnosis. Herein, we reflect on how the pandemic has impacted *A&R*, the medical publishing world, and how we may best engage our community to navigate current challenges.

Two "front page" rheumatology examples and how their stories progressed demonstrate the infodemic: hydroxychloroquine and the cytokine storm.

Hydroxychloroquine, a drug that has both antimicrobial and immunomodulatory properties, was widely touted as a cure or preventative treatment for COVID-19. As rheumatologists know too well, the resulting demand for hydroxychloroquine squeezed supply, impacting our patients who have benefitted from the drug for decades. The rationale behind the hydroxychloroquine excitement was limited to in vitro activity against severe acute respiratory syndrome coronavirus 2 (SARS–CoV-2), together with a small uncontrolled study (1,2). When people are dying, doctors need to act upon the best data available, even when those data are weak. Small case series led to larger observational studies, with comparator patients who did not receive hydroxychloroquine (3). Randomized controlled trials (RCTs) were begun to put the hypotheses to the test. However, as the observational studies grew in size and rigor, the results became less encouraging (4); not surprisingly, RCT results matched the negative observational studies (5).

The cytokine storm remains a more complex story. Infection with any pathogen elicits an immune response, sometimes resulting in more harm than good. The "storm" metaphor is appropriate when inflammation becomes self-sustaining, driven primarily by cytokines and other immune signals rather than by the original trigger. Many reviews examined whether severe COVID-19 represented a vicious circle of this kind, including one in the pages of *A&R* that explicitly highlighted both what we know and what we don't (6). Immunosuppression helps some patients with COVID-19, as shown most clearly by the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial, which found that dexamethasone reduced mortality in patients requiring respiratory support (7). Blockade of the cytokines interleukin-6 (IL-6) and IL-1 has been supported at the case series level, although hydroxychloroquine illustrates the potential pitfalls of uncontrolled observational data in a disease that has a variable and unpredictable course. Multisystem inflammatory syndrome in children (MIS-C) does appear to be a bona fide postinfectious process induced by SARS–CoV-2, appearing in the pediatric population weeks after acute COVID-19 has peaked in adults and responding (again at the anecdotal level) to intravenous immunoglobulin (IVIG), glucocorticoids, and other immunosuppressants (8).

Do these syndromes reflect cytokine storm? Many distinct conditions fall under this umbrella term (6). At the core of most cytokine storms is a macrophage–lymphocyte amplification loop, wherein activated macrophages stimulate lymphocytes that in turn elaborate macrophage-activating cytokines, in the absence of adequate counterregulatory signals. Whether SARS–CoV-2 triggers such a loop remains uncertain. Elevation of ferritin, D-dimer, the interferon-γ marker CXCL9, and the T cell activation product soluble CD25 suggests such a possibility, but the levels observed typically do not approach those seen in more archetypal cytokine storms (9). Further work will be required to determine

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whether SARS–CoV-2 initiates a different kind of cytokine storm, or whether these markers of inflammation simply reflect the immune response elicited by the virus directly and through the endothelial injury it produces.

Three questions raised by these examples shine a light on the infodemic: 1) Did the scientific process during this phase of the COVID-19 pandemic progress in an appropriate manner? 2) Was the science reviewed using appropriate methods? And, 3) how should the information arising from these studies be effectively managed and communicated?

Scientific process

Few activities, including science, are best conducted as a "sprint." However, the COVID-19 pandemic killed so many people that speed was necessary. Gathering all the usual supportive data—biomarkers, pharmacodynamics, safety in the target population—was compressed or neglected, albeit with the best of intentions, in the effort to repurpose rheumatic disease drugs for COVID-19. The hydroxychloroquine and anticytokine scientific stories have some differences in this respect, but many similarities.

Hydroxychloroquine has known effects on malaria as well as several less common pathogens. A small literature suggested that it might have activity against SARS–CoV-2, but no clinical studies had been conducted. As hydroxychloroquine is an approved drug with a relatively good safety profile, clinicians watching patients die of COVID-19 were understandably eager to grasp at this straw. From these early uncontrolled experiences, observational studies were conducted with mostly negative results and trials were organized (5). The trials showed no benefit and possible risk, and most have been shut down.

The cytokine storm story has yet to play out. Enthusiasm for IL-6 blockade continues, perhaps at a slightly diminished pitch because of the early termination of several trials due to futility, although others remain in progress or have shown promising results (10). Randomized studies of IL-1 blockade and other immunomodulators are in progress. Notably, there is now evidence that dexamethasone may save lives, supporting the general principle that immunosuppression could be a viable approach to severe SARS–CoV-2–related illness. In MIS-C, physicians will need to act on the basis of immunologic principles together with experience gathered in the clinic. The American College of Rheumatology (ACR) guidance recommends consideration of IVIG, glucocorticoids, and, in severe cases, the IL-1 blocker anakinra (8). Recognizing again the limits of observational data, this is all we will have until randomized trials are conducted.

Scientific review

The review of science has an orthodoxy that at first blush seems unfit for a pandemic. It is by necessity deliberate, with a role for editors, peer reviewers, discussion, and revision. The key questions—is the submitted science innovative, rigorous, and well presented?—take time to answer. Why should these questions and processes slow science during a pandemic? We suggest that it is for the same reason as the imperative for speed: because so many lives are at stake.

Many authors of COVID-19 papers can offer how the traditional review process did not work for them. It was too slow, too picky, and may have hindered progress. All of these criticisms are fair and to some extent true. Like many journals, *A&R* was overwhelmed with COVID-19 submissions. Nevertheless, *A&R* responded, and COVID-19 papers (82 papers through July 27, 2020) have had a first decision in an average of 7 days. Our reviewers, often themselves overextended by the exigencies of COVID-19, stepped up to answer our call for quick but thorough reviews. Accepted papers have been posted online almost immediately and free of charge.

The rush to publish in the COVID era has had some unfortunate consequences. While retractions will always be a part of scientific publishing, a few high-profile retractions of COVID-19 papers (11,12) have left the public unsure as to what to believe, reducing their confidence in the medical profession. Disputes between authors of COVID-19 papers have spilled into the lay press, allowing the public to see that human foibles affect us all.

Scientific communication

Perhaps the most difficult aspect of the infodemic is how to effectively present the peer-reviewed science to the public. *A&R* has a historic tradition of peer review and publishing that has served rheumatology well, but much less expertise at messaging the science to the lay public. Some might suggest that this is not the journal's role, but during the pandemic are we not all responsible for the information being put out in the media? *A&R* offers press releases for many of our articles, and for almost all regarding COVID-19. We will help put journalists in touch with authors. As many know, we have worked to make the science in all of the ACR journals more accessible through social media, including encouraging authors to create a video describing the science that is hosted on the journal website. We have not attempted to directly communicate with patients or the public at large. Should *A&R* or the ACR make public communication a greater part of our agenda?

During COVID-19, communication with the public has been a major difficulty. Most of the problems have been with inconsistencies in simple messages: "wear a mask," "get tested if you display any symptoms," "do not drink chlorine bleach" (no, chlorine is not the same as hydroxychloroquine). Some of the communication problems have been with complex scientific issues: Does hydroxychloroquine work to prevent or treat COVID-19? Are nonsteroidal antiinflammatory drugs dangerous to people with COVID-19? Should disease-modifying antirheumatic drugs

be discontinued to prevent an infection or during a known infection? These are questions with evolving answers that have been the focus of ongoing studies. Good public health messaging without adequate data is fraught. Should the journal add to the cacophony of COVID-19 communication?

A&R has stuck with the fundamentals that we do well: review, edit, and publish science. We work to make our reviewing responsive to the needs of the community, finding relevant experts who give constructive feedback in a timely manner. Editing and publishing have been appropriately sped up. However, we will continue to maintain our high standards. We have been reminded over the last few months that science is an imperfect process, but that with careful attention to accumulating data, it becomes a self-correcting one. As *A&R*'s editorial board enters a new era, we welcome the input of our readers as we continue to work toward the benefit of the community of patients and physicians we serve.

AUTHOR CONTRIBUTIONS

All authors drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

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