Editorial Commentary

Interferon beta in COVID-19: a landmark looming in the uncharted sea of COVID-19?

Carlo Bosi[1], Andrea Gori[2], Mario Raviglione[2]

[1]University of Milan, Medical School, Milan, Italy; [2]University of Milan, Centre for Multidisciplinary Research in Health Science (MACH), Milan, Italy
Correspondence to: Carlo Bosi. University of Milan, Medical School, Milan, Italy. Email: carlo.bosi@studenti.unimi.it.

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The coronavirus disease-2019 (COVID-19) epidemic was officially recognized in December 2019 (1). The etiological agent—severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)—was first identified in Wuhan, Hubei, China as a member of the *Sarbecovirus* genus of the *Coronaviridae* family (2). The animal source of the virus remains controversial (3).

The virus spread rapidly throughout China and other countries in early 2020. As of 4 March 2020, 93,091 cases and 2,984 deaths have been confirmed globally. Local transmission is being reported in an increasing number of countries, including those located in South America and the African Region, making it de facto a pandemic (4).

Blocking transmission through preventive measures, proper surveillance, rapid identification of the infected person and isolation of the patient and his close contacts are the basic approaches to tackling the COVID-19 epidemic. A series of strategies for disease prevention and control in both community and healthcare settings has been defined by the World Health Organization. These include: (I) basic protective measures: washing hands frequently, maintaining social distancing, avoiding touching eyes, nose and mouth, and practicing respiratory hygiene; (II) use of masks during home care and in health care settings; (III) clinical management (5); (IV) infection prevention and control in health care settings (6); and (V) home care for patients with suspected novel coronavirus infection (7). Epidemic management via contact tracing and case isolation appears however insufficient to control outbreaks, according to a recently proposed model (8), especially if transmission occurs in the asymptomatic phase of the disease. Enforcing stricter rules on quarantine of potentially infected people and implementing social limitations might indeed be necessary. Should all those strategies be unsuccessful, response interventions would then be aimed at controlling and mitigating the disease. In this scenario, intrinsic weaknesses of the health care system, such as insufficient healthcare capacity and scarcity of intensive care units (ICU), would likely become a bottleneck to proper disease management. Implementing therapeutic options to cure people, reduce suffering and deaths, and simultaneously reduce days of recovery is therefore imperative, especially for those countries where the epidemic is expanding rapidly and where hospitalizations are on the verge of overburdening health services.

Currently, COVID-19 treatments can be classified in two main categories: virus- and host-based. In both cases, one can employ either investigational agents or repurpose approved medications. Although newly defined investigational drugs would potentially include structural biology studies, functional preclinical testing, and validation in clinical trials, and thus could be predicted to be highly efficacious, their development would require a longer time span. Instead, drug repurposing might provide three major advantages: (I) safety and tolerability data would be available, thus speeding up their use in clinical trials; (II) medications might be marketed by different companies and include generics or biosimilars, granting affordable prices for public authorities; (III) accessibility is rapid and larger, compared to that of novel investigational drugs.

Amongst the candidates to be part of future regimens, those prioritized by the WHO R&D blueprint as the most promising include remdesivir, lopinavir/ritonavir (LPV/RTV), and interferon beta (IFNβ) (9).

Remdesivir is a broad-spectrum antiviral agent, with proven activity against coronaviruses (10). In addition, it has been reported that a COVID-19 patient recovered after Remdesivir intravenous administration (11). Because

of this, the drug is currently being tested in COVID-19 patients against standard of care in two phase III trials (NCT04292899 and NCT04292730) and against placebo in one phase II trial (NCT04280705). Results should become available soon.

LPV/RTV is a combination regimen approved for human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS). In the 2003 SARS epidemic, LPV/RTV was reported as producing a favorable clinical response (12). Recent data demonstrate that it is not efficacious in COVID-19 (13).

IFNβ, a member of the type I interferon (IFN-I) family, is currently approved in the form of a recombinant protein in the European Union and the United States for the treatment of multiple sclerosis. It is presently marketed in two forms: IFNβ 1a, and IFNβ 1b, which, from a clinical point of view, have similar safety profiles (14).

Among the available repurposed agents for the treatment of COVID-19, we believe that IFNβ, and in particular IFNβ 1b, stands out for having the most solid biological rationale. Indeed, it could exert direct antiviral effects and immunomodulating activities, and may overcome the general ability of coronaviruses to escape immune recognition via suppression of IFN-type I expression by the host (15).

Although a preclinical model for SARS-CoV-2 currently is not available, useful hints are provided by those based on severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). IFNβ antiviral effects have been extensively investigated in preclinical studies, both *in vitro* on infected human cell lines, and in animal studies. *In vitro*, IFNβ 1b displayed an antiviral activity superior to that reported for interferon α (IFNα) and interferon gamma (IFNγ) in SARS-CoV-infected human epithelial cells (16). In the case of MERS-CoV-infected human epithelial cells, IFNβ 1b demonstrated antiviral activity, which was superior to that seen with LPV/RTV. The same study reported efficacy of IFNβ 1b combined with LPV/RTV in a mouse model of MERS infection: the combination improved pulmonary function in therapeutic settings, although it failed to diminish signs of acute lung injury (17). In rhesus macaques, which might better resemble MERS pathogenesis in humans, a study reported that interferon-α2b (IFN-α2b) and ribavirin improved the clinical outcome of MERS-CoV infected primates (18). Having IFNβ 1b a lower EC_{50} relative to IFN-α2b (19), it is reasonable to hypothesize that IFNβ 1b could be more potent in those infected with MERS.

In the clinical settings, IFNβ has not been used against SARS, but evidences could be in place for MERS. In a retrospective study, the efficacy of recombinant IFN-α2a, IFN-α2b, and IFNβ 1a was studied in critically ill MERS patients. Although, no differences were noted in 90-day mortality or in MERS-CoV RNA clearance (20), most likely due to drugs not reaching the effective EC_{50} in vivo, data supported the start of a clinical trial testing the combination of IFNβ 1b and LPV/RTV in MERS (NCT02845853). The rationale was based on the assumption that the EC_{50} for IFN1b is lower than that of other IFN-I formulations (19).

The putative therapeutic value of IFNβ 1b in the case of SARS-CoV-2 could be inferred from recently published data generated by the analysis of clinical specimens. Huang and co-authors compared the serum cytokine profile of COVID-19 patients admitted or not to the ICU with that of healthy controls and showed that COVID-19 patients were characterized by abnormal elevation of pro-inflammatory cytokines and chemokines (21). We believe that a closer look at the immune profile possibly highlights "*defective type I interferon responses*" and "*detrimental inflammation*". Such profile could be indirectly inferred by the following:

(I) Higher TNFα and IFNγ levels in COVID-19 patients compared to healthy controls might depict *defective type I interferon responses* (22,23);

(II) Higher TNFα, IL-4, IL-8, IL-17, G-CSF, GM-CSF, IL-10, MCP-1, MIP-1a, and MIP-1b in COVID-19 patients compared to healthy controls, would define *detrimental inflammation*. This assumption is further strengthened by the finding that TNFα, IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, and MIP-1 levels are increased in ICU patients compared to non-ICU ones, supporting the concept that the worst clinical outcome is accompanied by a more severe inflammatory response.

We speculate that the cytokine/chemokine expression pattern might reflect a neutrophil-based inflammatory response, which would explain the lung-tissue injury typical of COVID-19. Histological studies would address this possibility.

Thus, together available data and educated guess suggest the use of IFN type I, and in particular of IFNβ 1b, in the treatment of COVID-19. Several points would need to be taken into consideration. These include timing and dosage.

Timing of administration should be carefully evaluated, given the notion that although type I interferons exert a negative regulator effect on many inflammatory

cytokines (24), their effects might vary according to the immune context and type of viral infection. The complex immunomodulatory actions of type I IFNs have been investigated in many animal models of infection, including those of HIV, *hepacivirus C* (HCV), and *lymphocytic choriomeningitis mammarenavirus* (LCMV) (25). Unfortunately, none of them finely recapitulates SARS-CoV-2. According to a proposed model, type I IFN dynamics follow a rapid increase upon viral infection and decrease within one week. It is unclear whether preventing this decrease would help control the infection in its acute phase. On the other hand, in the context of chronic infection, type I interferons may dampen the antiviral response and promote inflammation (25).

Based on the present data, we speculate that in the case of COVID-19 patients, IFNβ 1b immunomodulatory activity might be of maximal value in recently infected patients, in which it might promote optimal viral control. Whether those that have been infected for weeks might benefit from type IFN therapy is difficult to determine with available evidences.

With respect to dosage, we would like to point out that although it might be questioned whether the EC_{50} for IFNβ 1b direct anti-viral activity could be reached *in vivo* in the absence of toxicity, immunomodulating effects might be reached at much lower doses, as shown in MERS animal studies (17,18). We speculate that based on these evidences a trial combining IFNβ, ribavirin and LPV/RTV was recently initiated in COVID-19 patients (NCT04276688).

In conclusion, we believe that available knowledge advocates the importance of challenging these concepts with the analysis of COVID-19 clinical specimens that should soon become available. In addition, testing IFNβ 1b activity and efficacy in the setting of COVID-19, either alone or in combination with the antivirals currently prioritized by the World Health Organization is urgent. We underline that, as we navigate in the unknown, the treatment of COVID-19 should follow those landmarks that stand on most solid biological bases. IFNβ 1b could be one of them.

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References

1. WHO. Pneumonia of unknown cause – China. WHO. 2020. Available online: https://www.who.int/csr/don/05-january-2020-pneumonia-of-unkown-cause-china/en/
2. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 2020;382:727-33.
3. Cyranoski D. Mystery deepens over animal source of coronavirus. Nature 2020;579:18-9.
4. WHO. Coronavirus disease (COVID-2019) situation reports. [cited 2020 Mar 5]. Available online: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports
5. WHO. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected. [cited 2020 Mar 6]. Available online: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected
6. WHO. Infection prevention and control during health care when novel coronavirus (nCoV) infection is suspected. [cited 2020 Mar 6]. Available online: https://www.who.int/publications-detail/infection-prevention-and-control-

during-health-care-when-novel-coronavirus-(ncov)-infection-is-suspected-20200125
7. WHO. Home care for patients with COVID-19 presenting with mild symptoms and management of their contacts. [cited 2020 Mar 6]. Available online: https://www.who.int/publications-detail/home-care-for-patients-with-suspected-novel-coronavirus-(ncov)-infection-presenting-with-mild-symptoms-and-management-of-contacts
8. Hellewell J, Abbott S, Gimma A, et al. Feasibility of controlling COVID-19 outbreaks by isolation of cases and contacts. Lancet Glob Health 2020. doi: https://doi.org/10.1016/S2214-109X(20)30074-7.
9. World Health Organization. (2020). WHO R&D Blueprint: informal consultation on prioritization of candidate therapeutic agents for use in novel coronavirus 2019 infection, Geneva, Switzerland, 24 January 2020. World Health Organization.
10. Sheahan TP, Sims AC, Graham RL, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med 2017. doi: 10.1126/scitranslmed.aal3653.
11. Holshue ML, DeBolt C, Lindquist S, et al. First Case of 2019 Novel Coronavirus in the United States. N Engl J Med 2020;382:929-36.
12. Chu CM, Cheng VC, Hung IF, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax 2004;59:252-6.
13. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med 2020;382:1787-99.
14. Smith B, Carson S, Fu R, et al. Drug Class Review: Disease-modifying Drugs for Multiple Sclerosis [Internet]. Drug Class Reviews. Oregon Health & Science University. Available online: http://www.ncbi.nlm.nih.gov/pubmed/21348046
15. Vijay R, Perlman S. Middle East respiratory syndrome and severe acute respiratory syndrome. Curr Opin Virol 2016;16:70-6.
16. Cinatl J, Morgenstern B, Bauer G, et al. Treatment of SARS with human interferons. Lancet 2003;362:293-4.
17. Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun 2020;11:222.
18. Falzarano D, de Wit E, Rasmussen AL, et al. Treatment with interferon-α2b and ribavirin improves outcome in MERS-CoV-infected rhesus macaques. Nat Med 2013;19:1313-7.
19. Chan JF, Chan KH, Kao RY, et al. Broad-spectrum antivirals for the emerging Middle East respiratory syndrome coronavirus. J Infect 2013;67:606-16.
20. Arabi YM, Shalhoub S, Mandourah Y, et al. Ribavirin and Interferon Therapy for Critically Ill Patients With Middle East Respiratory Syndrome: A Multicenter Observational Study. Clin Infect Dis 2019. doi: 10.1093/cid/ciz544.
21. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
22. Ivashkiv LB, Donlin LT. Regulation of type I interferon responses. Nat Rev Immunol 2014;14:36-49.
23. Teles RM, Graeber TG, Krutzik SR, et al. Type I interferon suppresses type II interferon-triggered human anti-mycobacterial responses. Science 2013;339:1448-53.
24. Kalliolias GD, Ivashkiv LB. Overview of the biology of type I interferons. Arthritis Res Ther 2010;12 Suppl 1:S1.
25. Snell LM, McGaha TL, Brooks DG. Type I Interferon in Chronic Virus Infection and Cancer. Trends Immunol 2017;38:542-57.

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