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Should interferons take front stage as an essential MS disease-modifying therapy in the era of coronavirus disease 2019?

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In the unprecedented pandemic of the coronavirus disease 2019 (COVID-19) along with a limited clinical understanding on effective vaccines and therapies, there are currently many unknowns for patients with autoimmune conditions, such as MS, who require ongoing treatment with immunotherapies. As information is currently lacking on the immune effects of COVID-19 in the context of MS disease-modifying therapies (DMTs), a challenging clinical question being faced by patients and neurologists is whether to continue current DMTs for patients with MS and risk potentially greater morbidity and mortality due to COVID-19 infection vs discontinue DMT therapy and risk MS disease relapse. At this time, we desperately need data to guide which DMTs may best treat both COVID-19 and MS.

Impressively, there has been a rapid international medical response in repurposing several antiviral therapies toward COVID-19 treatment, including remdesivir, lopinavir, ritonavir, ribavirin, interferon-alpha (IFN-α), and interferon-beta (IFN-β)[1,2] (NCT04315948). Type I interferons such as IFN-β are of particular interest for patients with MS because these DMTs have been Food and Drug Administration-approved for use in MS since the 1990s.[3] Interferons were originally discovered to "interfere" with viral replication and are classified as type I (IFN-α, β, and ω), type II (IFN-γ), or type III. In the human IFN-α family, there are 13 genes encoding several isoforms, many of which have been popularized for treatment. By contrast, human IFN-β is encoded by only 2 genes with a more limited number of commercially available recombinant isoforms. Between the type I interferons, IFN-β has been primarily used in MS, whereas IFN-α has been commonly used in the treatment of viral infections, such as herpes zoster, hepatitis B and C, and HIV. However, there is also evidence to suggest that IFN-α may have beneficial effects in MS. For example, treatment with IFN-α2a can lead to a reduction in MRI disease activity in patients with MS with neutralizing antibodies to IFN-β.[4]

Different IFN-α and IFN-β isoforms are currently being evaluated and compared for the treatment of COVID-19. Interferon signaling pathways seem to be significantly upregulated, especially during the most critical stages of pulmonary disease, with IFN-α serum levels correlating with disease severity during the peak of disease.[5,6] Similarly, circulating IFN-β has also been reported to increase during peak disease stages although IFN-β levels remain elevated even after symptomatic improvement.[5,6] These data suggest that IFN-α may have a key role in the reduction of the viral load during the peak of the COVID-19 disease, whereas IFN-β may have a potential role in the reduction of viral replication over the entire course of the disease. Because interferons are known to induce different cytokines and genes in different cell types and organs, one important caveat to consider is the timing of interferon administration in COVID-19 and the possibility of dichotomous interferon effects during early vs later stages of the disease.

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IFN-α has already been used as an active treatment for COVID-19 in China.[1] Both nebulized and subcutaneous forms of recombinant IFN-α, IFN-β1a, and IFN-β1b are also currently tested in COVID-19 clinical trials in combination with other therapeutics (NCT04315948, NCT04276688, NCT04293887, NCT04251871, and NCT04275388).

One of the largest current trials, the World Health Organization multinational SOLIDARITY trial, is currently evaluating 4 therapeutic regiments including (1) IFN-β with ritonavir/lopinavir, (2) ritonavir/lopinavir without IFN-β, (3) chloroquine or hydroxychloroquine, and (4) remdesivir.[2] Of note, nebulized preparation of IFN-α has been reported to improve delivery to the respiratory tract while also reducing common interferon side effects, such as fatigue and myalgias, symptoms that can also be a part of COVID-19 infection.

Although interferon therapies revolutionized MS management in the 1990s, more recently, interferons have been relegated to the backstage of the MS DMT armamentarium because of the emergence of more effective and better tolerated DMTs. Nevertheless, given the potential benefits of interferons in the treatment of COVID-19, an important question now is whether interferons should be again brought to the front stage of MS management. If data from ongoing clinical trials continue to support the benefit of interferons in the treatment of COVID-19, it is perhaps prudent to consider interferons as a first-line therapy in newly diagnosed patients with MS. In patients with MS on other DMTs, we could consider changing therapy to interferons or adding interferon therapy to the patient's current DMT. For patients with active MS, other potential treatment strategies may be to combine interferon therapy with pulsed intermittent corticosteroids or IV immunoglobulin given monthly to quarterly or with a DMT that has antiviral properties (e.g., teriflunomide[7]). In the latter case, a carefully formulated treatment plan tailored to the patient could provide a strategic advantage over cell depleting MS DMTs by virtue of the inherent multiplicity of actions of type I IFNs when used as part of combination therapy.

There are of course many unknowns regarding whether IFN-β or IFN-α therapies would be effective in the management of COVID-19 and MS and which specific IFN-β and IFN-α isoforms may best create this balance. It will also be important to continue to assess how treatments such as IVIG and steroids may impact MS and COVID-19. Furthermore, treatment decisions will vary depending on patient age, disease activity, comorbidities, and current DMT. Nevertheless, based on the long-standing clinical experience and long-term safety profile of IFN-β use in patients with MS, interferons could be a critical therapy to treat both COVID-19 and MS during the unprecedented international pandemic, and we should reconsider interferons' place in the MS DMT armamentarium.

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