Future Perspectives

Researching COVID-19 in progressive MS requires a globally coordinated, multi-disciplinary and multi-stakeholder approach—perspectives from the International Progressive MS Alliance

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Abstract

Background: The COVID-19 pandemic has reinforced the importance of research for the health of our society and highlighted the need for stakeholders of the health research and care continuum to form a collaborative and interdependent ecosystem.

Objective: With the world still reeling from waves of the COVID-19 pandemic and adapting to the vaccine rollout at widely different rates, the International Progressive MS Alliance (hereafter Alliance) organized a meeting (April 2021) to consider how the Covid-19 pandemic impacts the health and well-being of people with progressive Multiple Sclerosis (MS).

Methods: We invited the Alliance stakeholders and experts to present what they have learned about SARS-CoV-2 infection and progressive MS and to define future scientific priorities.

Results: The meeting highlighted three priorities for additional focus: (1) the impact of Disease Modifying Therapies (DMTs) on the risk of COVID-19 and on the efficacy of COVID-19 vaccines in people with progressive MS; (2) the long-term impact of COVID-19 and COVID-19 vaccines on the biology of progressive MS; and (3) the impact on well-being of people with progressive MS.

Conclusion: This paper's calls to action could represent a path toward a shared research agenda. Multi-stakeholder and long-term investigations will be required to drive and evolve such an agenda.

Keywords: Multiple sclerosis, progression, COVID-19 pandemic, multi-stakeholder agendas

Introduction

Multiple Sclerosis (MS) is a growing global neurological challenge affecting 2.8 million individuals worldwide.[1] A large proportion of these individuals either live with a relapsing form (RRMS) or a progressive form of MS—the latter either Primary Progressive MS (PPMS) which is progressive from the outset, or Secondary Progressive MS (SPMS) which evolves from RRMS over the course of 10–20 years and is characterized by the gradual worsening of the disease with or without superimposed relapses. Progressive forms of MS are characterized by steady progression and accumulating disability independent of acute inflammation and relapses.[2]

People with progressive forms of MS (PwPMS), due to the nature of their disease, tend to have worse disability and poorer health, which could contribute to SARS-CoV-2 infection severity.[3] Some investigations have shown that people with MS who develop more severe COVID-19 tend to be older, to suffer from progressive disease and have a higher degree of disability.[4,5] Quickly after the pandemic began, researchers from many different networks collected data on outcomes of SARS-CoV-2 infection for people living with MS (PwMS).[6–10] So far, several risk factors for more severe outcomes from SARS-CoV-2 infection have been identified,[4] including older age, higher

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disability, cardiovascular comorbidities, obesity and possibly male gender.

Since 2012 the Alliance has been investing in a global research strategy[11] to expedite the development of disease-modifying and symptom-management therapies for people living with progressive MS. It will be critical for short term decision making that PwMS and their care providers understand the interactions between SARS-CoV-2 infection, vaccination and Disease Modifying Therapies (DMTs) on disease progression, as well as being vital for Industry's continued efforts to discover and develop therapies for PwPMS.Within this framework, the Alliance Industry Forum,[12] in its advisory role to the Alliance's Scientific Steering Committee, organized a meeting (April 2021) to discuss with major Alliance stakeholders and experts what we have learned about SARS-CoV-2 infection, the Covid-19 pandemic and progressive MS.

During the meeting, several areas were discussed and highlighted for further study.

Challenges and opportunities

Impact of disease modifying therapies (DMTs) on the risk of COVID-19 and on the efficacy of COVID-19 vaccines in people with progressive MS. PwPMS faced several challenges during the pandemic. One challenge is reducing the risk of SARS-CoV-2 infection through multiple measures including masking, social distancing, and hand hygiene. For PwMS, particularly those with greater disability, comorbid health conditions or more advanced age, minimizing the risk of virus exposure is pivotal and particularly in the face of new variants of SARS-CoV-2 with significant impact on transmissibility, severity and/or immunity. It is, however, important to consider that steps to minimize viral exposure can lead to social isolation and declines in mental health. Another challenge is to ensure that PwPMS are vaccinated and that they receive booster doses according to the evolving guidelines. We need to understand the impact of SARS-CoV-2 variants in the context of vaccination schedules to inform decisions such as the need for and timing of re-immunizations. Managing these challenges, and other challenges emerging based on evidence of how the Covid-19 pandemic affects people with MS, requires that global COVID-19 advice be updated frequently and distributed widely. Initial guidelines[13] were developed and updated by MS clinicians and research experts in collaboration with patient organizations.

Recent studies revealed that the anti SARS CoV2 antibody titer induced by vaccination could be influenced by the type of DMT being used by the PwMS.[14,15] No evidence of an impact of vaccination on disease severity has been reported.[16] There are several key opportunities to better achieve optimal management strategies for PwMS during the pandemic. We need to ensure that the MS community understands that, to date, no association has been shown to exist between Covid-19 vaccination and worsening of MS disease or increased risk of relapses. This fear drives some MS patients away from vaccination, putting them at risk for SARS-CoV-2 infection and subsequently for developing severe forms of infection. In addition, evidence presented during the meeting showed fewer clinical visits for PwMS and fewer new diagnoses, since the pandemic began highlighting that early treatment may be delayed or treatment optimization delayed, resulting in long term effects on progression. A cross-sectional survey of adult PwMS was performed online, using the U.S.-based patient-powered iConquerMS™ platform, in April 2020.[17] Of the 1019 participants analyzed, 650 (64%) reported canceling or postponing medical visits. Of these 650, 222 (34% of 650) reported canceling a neurologist's visit, 112 (17%) an MRI, 499 (77%) a non-neurologist medical visit, and 212 (33%) a laboratory visit. For these participants, ocrelizumab was the most difficult to access and delayed DMT, with a total of 42 (38%) participants describing difficulties related to the drug (2 with prescription, 19 with infusion, and 21 with monitoring tests).

The long-term impact of COVID-19 and COVID-19 vaccines on the biology of progressive MS. To comprehend the interplay between SARS-CoV-2 infection and progressive MS, it will be important to understand whether and how the biology of the infection intersects the biology of MS. One of the most informative efforts for the definition of the immunogenetic basis of SARS-CoV-2 infection is evaluating how genetically determined errors of the immune response may favor an aggressive course of COVID-19.[18] Interestingly, a defective type 1 interferon response was the first mechanism to be identified, suggesting the hypothesis that interferon-beta, an established therapy for MS, may help modulate the aberrant immune response in specific phases of SARS-CoV-2 infection.[19] Another element of interest for the pathophysiology of MS is the massive T cell activation, immune senescence, and skewing toward an inflammatory Th17 phenotype induced by SARS-CoV-2 pneumonia.[20] Here, in addition to the obvious potential consequences of an activation of

the immune response, the mechanism that may specifically affect progressive MS is immune senescence, a process described in MS as well as in aging.[21,22] Current efforts are concentrated on the definition of the duration of the protection in people with dysfunction of the immune system, undergoing immunosuppressive therapies.[23] We must also better define the timing of vaccination in relation to dosing MS therapies, including steroids and encourage Industry's and other stakeholders continued efforts to support pandemic preparedness research and support real world data efforts in MS registries to monitor the safety of MS therapies in the context of COVID-19.

Impact of the COVID-19 pandemic on well-being of people with progressive MS. Emerging research indicates that in addition to physical and cognitive deficits, PwMS have to contend with various psychiatric symptoms.[24] Among psychiatric symptoms, however, mood disorders, such as depression and anxiety, occur at much higher prevalence in PwMS than in the general population. Lifetime prevalence of major depression in PwMS is estimated to be 25–50%, a number two to five times greater than in the general population, and more than 50% of MS patients present with some type of cognitive decline during the course of the disease.[25] Anxiety has been reported to be present in up to 22.1% of PwMS. These conditions can compromise their ability to adjust to, and cope with, stressful life events such as the pandemic with all its attendant risks and restrictions.[26,27] The challenge for health care professionals is to identify those PwMS at risk whose coping resources have proven inadequate. It is therefore a priority that health professionals carefully monitor the mental health of PwMS during the pandemic. MS specialists should adapt a strategy to monitor MS patients for neuropsychiatric complications and also to use applicable treatment options. When planning support strategies special attention should be placed on patients more at risk to develop cognitive and neuropsychiatric complications, including patients with higher level of disability, those who are taking immunosuppressive therapies, patients at a progressive stage and those with comorbid medical conditions.[28] Disentangling the influences of the pandemic from the natural history of MS on the mental health of PwMS can prove difficult. However, if there is a clear temporal association between pandemic linked restrictions and a deterioration in a person's mood, for example, the causal association is strengthened.[29] Exploring this facet of the pandemic on PwPMS should be a priority for the scientific community.

Given the complexity of MS, it is important for the behavioral specialists to work closely with neurologists and other members of the interdisciplinary team. Having clinical input from these different specialities will help tailor the interventions to meet specific challenges—such as neuropsychiatric complications—that may, or may not, be pandemic related. However, there is emerging pandemic related data that highlights the resilience in certain subgroups of PwMS. For example, a longitudinal behavioral study of PwPMS did not show a deterioration in mood, anxiety or quality of life compared to pre-pandemic indices.[30,31] A different picture emerged, however, in people with RRMS, where a deterioration across all these indices was noted.[32,33]

Finally, one of the important, positive offshoots of the pandemic has been the effectiveness of e-health and telemedicine in assessing and managing anxiety and disorders of mood and cognition across the lifespan.[34,35] While these approaches are being used in PwMS,[36,37] findings as to their benefits are awaited. This presents the community with an opportunity to continue using these media to monitor PwMS more frequently, offer potentially effective pharmacological and rehabilitation treatments, and incorporate these platforms as an early warning system for clinical progression.[38,39] A recent consensus approach to assessing and managing people with MS has concluded that telemedicine is a feasible option and that patient reported outcome measures should be included in the process.[40] There is also preliminary data that such an approach can be effective in managing physical symptoms in those individuals with progressive disease.[41]

Call to action
We've entered a phase where initial knowledge gaps have been tackled and it is now important to provide strong support for research on the issues presented by this unprecedented viral pandemic. The actions linked to the defined scientific priorities are summarized in Table 1.

Action: further studies to understand the effects of DMTs, COVID-19 and vaccination on MS. It is critical to (a) continue to gather epidemiological data to better understand the factors (socio-demographic, clinical or DMTs) associated with the risk of contracting SARS-CoV-2 or developing severe disease.; and (b) sustain prospective efforts to monitor and clarify the impact of SARS-CoV-2 and COVID-19 vaccines on MS natural history (particularly on progression) and pathophysiology. If well conducted, such efforts

Table 1. Actions linked to the scientific priorities.

Strategic/scientific priority	Actions
To evaluate impact of SARS-CoV-2 on the health of persons with progressive MS	Prospective studies to monitor and clarify the impact of SARS-CoV-2 infection in persons living with progressive MS (MS related and non-MS related health outcomes)
To evaluate impact of DMTs on the severity of SARS-CoV-2 infection in persons with MS	Analysis of COVID infection severity in persons with progressive MS stratified by DMT exposures
To define the influence of DMTs on vaccine responses	Studies on antibody and cellular responses to the SARS-CoV-2 in vaccinated persons with MS
To evaluate whether COVID-19 vaccines and SARS-CoV-2 infection have a direct impact on the biology of progressive MS	Prospective studies to monitor and clarify the impact of SARS-CoV-2 infection and COVID-19 vaccines on MS natural history, pathophysiology and progression
To evaluate impact of COVID-19 on wellbeing of people with progressive MS	Studies on the effects of the pandemic on PwPMS neuropsychiatric complications and other dimensions of wellbeing (e.g. mobility, spasticity and fatigue). In particular, longitudinal data collection that distinguish between RRMS and PMS is a priority
To evaluate the impact of COVID-19 on patient reported outcomes—self-assessments of patient health status	Long-term follow-up studies to assess the effect of the COVID-19 pandemic on patient quality of life (link with global Patient Reported Outcome for MS Initiative).

could provide important insights into mechanisms of progression in MS. In addition, we need to understand the best means to maximize benefit from vaccination, and to support studies that are delving into both the antibody and cellular responses to the various COVID vaccine products. Data from this research will advance our understanding of immune-vaccine biology and will allow for more specific guidance on vaccination timing (particularly as a function of DMT selection) in the context of MS.

Action: further studies on well-being. More research is needed to fully gauge the effect that the COVID-19 pandemic is having on the functional domains of PwPMS, both during the pandemic and in the future. Physical, intellectual and social activities are all good for brain health, potentially boosting cognitive reserve. A sedentary lifestyle, which might have been caused or exacerbated by the pandemic restrictions,[42] could have exacerbated cognitive difficulties by reducing this reserve, as well as adversely influence mobility, spasticity and fatigue. To this end, Patient-Reported Outcome Measures (PROMs) provide the unique perspective of the patient on functional domains that matter most to them and efforts are ongoing to further advance the use of these

measures from research to care.[43–45] As part of this effort, PROMs will enable the long-term follow-up assessment of the impact of the COVID-19 pandemic on functional domains that are affecting PwPMS well-being, leveraging digital passive and active monitoring. In addition, longitudinal data exploring different effects of the pandemic on RRMS and PMS patients should be a priority. The MS behavioral data should also be interpreted alongside data from the healthy population at large, which speaks to heightened pandemic-related anxiety and depression in general, but with the added caveat that PwPMS have a significant, pre-existing behavioral vulnerability.[26]

Conclusion and recommendations
There is little doubt that the COVID-19 pandemic has been a transformational event. The cumulative loss of life and profound disruptions to societies and the global economy will reverberate for years to come. And yet the cumulative efforts of governments, the scientific community, industry and many others meaningfully altered the course of the pandemic and provided a model for the successful management of future globally disruptive diseases. As we look ahead, we can now take stock of the impact of the pandemic for PwPMS and the implications for

future efforts to understand progressive MS and develop treatment strategies for the disease.

Reflecting on the events of the last 24 months, we see several challenges and opportunities brought forward by the COVID-19 pandemic. One systemic challenge amplified by the pandemic is the inefficiency of our information-sharing systems particularly in relationship to the effect of DMT treatments on the severity of SARS-COV2 infections as well as on the disease course of MS, and now on vaccination. Clinical guidelines hastily developed with limited information and coordination contributed to an early confusing environment for patients and patient organizations. While eventually rectified through improved communication and coordination,[46] one can only wonder about the negative consequences of these initial uncoordinated efforts on PwPMS.

Another systemic challenge highlighted by the pandemic is the continued orientation of the scientific community (and supporting national organizations) towards individualized research and development agendas. While the MS community is indeed a global one, there is more work to be done to create an environment that favors rapid development of a global research and treatment agenda in response to transformative events. The desire to find answers about the effect of COVID-19 pandemic and SARS-COV-2 on PwPMS led to many disconnected research studies. While these individual efforts eventually yielded many important insights, there is an opportunity to consider whether an organized multi-stakeholder and multi-disciplinary framework could have ensured a more agile and coordinated response to the health challenges affecting PwPMS. In addition, the COVID-19 pandemic has illustrated the fragility of patient engagement in research and highlighted disruptions in care experienced by PwMS.[47–49]

Taken together these challenges may appear daunting but there is an opportunity for the global MS community to seize this moment and chart a new path. A collective and multi-stakeholder framework, such as the one used by the Alliance, could create the mechanism for meaningful engagement of patients in guiding a research and innovation agenda aimed to address the ongoing questions on COVID-19 and progressive MS, as well as on future scientific questions of importance to the progressive MS agenda. Such an effort could begin by facilitating a collective effort to evaluate systematically the impact of COVID-19 on PwPMS. This can include assessing the gaps in

sharing of data and information on progress, barriers and outstanding gaps between researchers, research funders and wider stakeholders. While this is an aspirational ambition, collective research efforts such as the International Progressive MS Alliance and the Global Patient Reported Outcomes (PROMS) initiative[50,51] have demonstrated the power of global research strategy development and associated coordination to address systemic gaps. The calls to action presented in this paper could represent the first path towards a shared research agenda.[52]

Declaration of conflicting interests

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Appendix—Alliance Scientific Steering Committee Roster (as of April 2021)

Bruce Bebo, Giampaolo Brichetto, William Carroll, Olga Ciccarelli, Timothy Coetzee, Giancarlo Comi, Anne Cross, Gabriele Dati, Alexis Donnelly, Anthony Feinstein, Robert J Fox, Emma Gray, Anne Helme, Reinhard Hohlfeld, Robert Hyde, Pamela Kanellis, Douglas Landsman, Catherine Lubetzki, Ruth Ann Marrie, Xavier Montalban, Julia Morahan, Lenka Ortner, Sarah Rawlings, Marco Salvetti, Finn Sellebjerg, Caroline Sincock, Kathryn Smith, Jon Strum, Alan Thompson, Clare Walton, Kathleen Zackowski, Paola Zaratin

Appendix—Alliance Industry Forum Roster (as of April 2021)

Shibi Belachew, David Brassat, Giancarlo Comi (Co-Chair), Licinio Craveiro, Fernando Dangond, Julie DeMartino, Rob Hyde (Co-Chair), Bruno Musch, Marco Salvetti, Nikolaos Sfikas, Kathryn Smith, Sana Syed, Davorka Tomic, Johan van Beek, Florian von Raison, Erik Wallstrom, Paola Zaratin.